(51) International Patent Classification 6 :		(11) International Publication Number:	**WO 98/35927**
C07C 29/03, C07D 401/14, 453/04	**A1**	(43) International Publication Date:	20 August 1998 (20.08.98)

(21) International Application Number: PCT/US97/02442

(22) International Filing Date: 14 February 1997 (14.02.97)

(71) Applicant *(for all designated States except US)*: THE SCRIPPS RESEARCH INSTITUTE [US/US]; 10550 North Torrey Pines Road, La Jolla, CA 92037 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: JANDA, Kim, D. [US/US]; 3181 Erie Street, San Diego, CA 92117 (US). HAN, Hyunsoo [KR/US]; 4120–85 Porte De Merano, San Diego, CA 92122 (US).

(74) Agents: LEWIS, Donald, G. et al.; The Scripps Research Institute, 10550 North Torrey Pines Road, TPC–8, La Jolla, CA 92037 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PEG–BOUND ALKALOID LIGANDS AND USE THEREOF

(57) Abstract

Polyethylene glycol monomethyl ether–bound alkaloid ligands (PEG–bound alkaloid ligands) are constructed and employed in the ligand–accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reaction (AD) with a range of olefins. The PEG serves as a scaffold which allows simple product separation, polymer–bound ligand recovery, and recycling of the chiral liquid phase support without a loss of catalytic activity or ligand acceleration.

PEG-BOUND ALKALOID LIGANDS
AND USE THEREOF

Description

Technical Field of the Invention:

The present invention relates to ligand-accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reactions (AD) of olefins. More particularly, the present invention relates to polyethylene glycol (PEG) bound alkaloid ligands employable in the ligand-accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reaction (AD) of olefins and to their synthesis and use.

Background of the Invention:

A variety of methods have been developed for recycling rare and/or valuable reagents and catalysts. In a conventional methodology, the reagent or catalyst is coupled to an insoluble support prior to its use in a reaction. After the reaction is complete, the reagent or catalyst is isolated and then recycled by isolating the insoluble support. The recycled reagent or catalyst attached to its insoluble support may then be re-employed in further reactions. Examples of this methodology have been developed for a number of reagents and catalysts. (Pittman et al. Comprehensive Organometallic Chemistry; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Mathur et al. Polymers as Aids in Organic Chemistry. Academic Press: New York, 1980; Frechet et al. Tetrahedron 1981, 37, 663; Sherrington et al. Syntheses and separations Using Functionalized Polymers; Wiley: New York, 1988; Bergbreiter et al. J. Polym. Sci., Polym. Chem. Ed. 1989, 27, 4205).

Although such insoluble reagents and catalysts are

successfully employed in many applications, there are recognized limitations associated with their use. (Barany et al. In The Peptides, Vol. 2; Gross, E.; Meienhofer, J., Eds.; Academic Press: New York, 1979, p.

5   1). The insolubility of the reagents and catalysts can be disadvantageous before, during, and after the reaction. Particular disadvantages include the following:

10   (1) Formation of the reagent or catalyst on the
          support can be more tedious.

      (2) Reagent or catalyst characterization is less than
          routine.

15

      (3) Insolubility can limit the range of substrates
          and/or the polymer-bound reagent/catalysts utility.

      (4) Insolubility can cause the reagent/catalyst
20   reactivity to behave somewhat differently than its
          soluble (solution) counterpart.

      (5) Non-linear kinetics have frequently been observed
          with insoluble supports.

25

      Because of the above disadvantages, alternative strategies have been developed for recycling valuable reagents and catalysts. In one successful strategy, the reagents or catalysts are supported by soluble
30   homopolymers. (Bayer et al. Angew.Chem. Int. Ed. 1975, 14, 493; Bayer et al. CHEMTECH 1976, 6, 212; Bergbreiter et al. ACS Symposium Series 1986, 308, 17; Bergbreiter et al. J. Am. Chem. Soc. 1987, 109, 174; Bergbreiter et al. CHEMTECH 1987, 17, 686; Phelps et
35   al. Tetrahedron Lett. 1989, 30, 3915; Bergbreiter et al. J. Org. Chem. 1989, 54, 2726; Bergbreiter et al. Tetrahedron Lett. 1991, 32, 2731; Doyle et al. J. Org.

Chem. 1992, 57, 6103; Bergbreiter et al. J. Am. Chem.
Soc. 1993, 115, 9295). In this strategy, the reactions
are carried out homogeneously, i.e., without an
insoluble phase, and the separation of the homopolymer
5   from reaction products is achieved by taking advantage
of the properties of the polymer chain. In the arena of
combinatorial synthesis, this strategy is termed "Liquid
Phase Combinatorial Synthesis" or LPCS. (Han et al.
Proc. Natl. Acad. Sci. USA 1995, 92, 6419.) The key
10   element of LPCS is a linear homopolymer, e.g.,
polyethylene glycol monomethyl ether (MeO-PEG), which
serves a dual role as both a terminal protecting group
and a solubilizing agent for any compound(s) synthesized
on the support. Combinatorial peptide, small molecule,
15   and peptidomimetic libraries can be synthesized using
this approach.(Han et al. J. Am. Chem. Soc. 1996, 118,
2539.)

The ligand-accelerated catalytic (LAC) asymmetric
20   dihydroxylation (AD) of olefins based on cinchona
alkaloid ligands was described by Sharpless in 1988.
(Jacobsen et al. J. Am. Chem. Soc. 1988, 110, 1968.)
Since this seminal report, the AD reaction has been
further developed to include application to a wider
25   range of olefins, improved enantiomeric efficiency, and
overall simplicity of operation (Kolb et al. Chem. Rev.
1994, 116, 2483). From the standpoint of cost, ligand
and/or metal recovery and recycling are of prime
interest because the cinchona alkaloid ligand and osmium
30   tetroxide are the most expensive components of the
procedure. Olefins have also been asymmetrically
dihydoxylated using insoluble polymer bound cinchona
alkaloid-ligands. (Kim et al. Tetrahedron Lett.. 1990,
31, 3003; Pini et al. Tetrahedron Lett. 1991, 32, 5175;
35   Lohray et al. Tetrahedron Lett. 1992, 33, 5453; Pini et
al. Tetrahedron: Asymmetry 1993, 4, 2351; Lohray et al.
Tetrahedron Lett. 1994, 35, 6559; Pini et al.

Tetrahedron 1994, 50, 11321; Pini et al. Tetrahedron
Lett. 1995, 36, 1549; Sung et al. Tetrahedron: Asymmetry
1995, 6, 2687). While this methodology represents a
major improvement with respect to convenience and

5   economics, it is deemed less than satisfactory because
of increased reaction times, highly variable yields and
lower enantioselectivity than had previously been
obtained with its solution phase counterpart. A report
by Salvadori and co-workers describes an insoluble

10   support that provides improved enantioselectivity.
However, their system still required long reaction times
(24 hours) and excess of polymeric ligand. Furthermore,
reaction yields were lower than observed under
homogeneous reaction conditions. (Petri et al.,

15   Chirality 1995, 7, 580.)

The problems associated with LAC in which the
ligand is localized by attachment to an insoluble
polymer can be understood by considering the basic tenet

20   upon which this concept is based (Berrisford et al.
Angew. Chem. Int. Ed. Engl. 1995, 34, 1059). During
LAC, the addition of a ligand increases the reaction
rate of an already existing catalytic transformation.
Both the ligand-accelerated and the nonaccelerated

25   reactions operate in solution simultaneously and in
competition with each other. If the ligand does not
have equivalent access to all the reaction compartments
where the substrate, metal oxidant and olefin reside,
the most fundamental requirement for a successful ligand

30   accelerated catalysis scenario is not met. For the
present case, this means that the chiral ligand resides
only in the insoluble phase while the OsO_4 and olefin are
in solution and free to react anywhere. In this
situation the optimal LAC conditions can probably never

35   be achieved even when using a large excess of the
insoluble polymer-bound ligand. (Petri et al. Chirality
1995, 7, 580.)

SUBSTITUTE SHEET (RULE 26)

- 5 -

Since its discovery in 1988, Sharpless' catalytic
asymmetric dihydroxylation (AD) of olefins has been
continuously refined by both a development of better
ligands and improvements in the secondary
5   oxidant/solvent system. (For review, see: Kolb et al.
Chem. Rev. **1994**, *116*, 2483; Becker et al. *Angew. Chem.
Int. Ed. Engl.* **1996**, *35*, 448). In parallel, Sharpless
(Kim et al. *Tetrahedron Lett.* **1990**, *31*, 3003) and other
groups (Pini et al. *Tetrahedron Lett.* **1991**, *32*, 5175;
10   Lohray et al. *Tetrahedron Lett.* **1992**, *33*, 5453.; Pini et
al. *Tetrahedron: Asymmetry* **1993**, *4*, 2351; Lohray et al.
Tetrahedron Lett. **1994**, *35*, 6559; Pini et al.
Tetrahedron **1994**, *50*, 11321; Pini et al. *Tetrahedron
Lett.* **1995**, *36*, 1549; Sung et al. *Tetrahedron: Asymmetry*
15   **1995**, *6*, 2687; Petri et al. *Chirality* **1995**, *7*, 580;
Song et al. *Tetrahedron: Asymmetry* **1996**, *7*, 645) have
investigated immobilization of these expensive ligands
onto insoluble polymer supports so as to aid in their
recovery. While this strategy provides a simple but
20   elegant way for automating the AD reaction, it has a
number of limitations including prolonged reaction times
and, more importantly, a reduction in enantioselectivity

What is needed is a soluble polymer-bound ligand
25   which provides all the advantages that an insoluble
support can offer including ease of product separation
and polymer-bound ligand recover/ reusability while also
being as effective as a free ligand both in reactivity
and selectivity. Furthermore, the new soluble polymer
30   bound-ligand system should be applicable to other
classes of AD ligands for improved enantioselectivity as
well as other enantioselective catalytic processes.

Brief Summary of the Invention:
35   The invention relates to polyethylene glycol
monomethyl ether-bound alkaloid ligands (termed liquid
phase ligands) which are constructed and employed in the

- 6 -

ligand-accelerated catalytic (LAC) Sharpless asymmetric
dihydroxylation reaction (AD) with a range of olefins.
These soluble polymer-bound ligands are much more
efficient than the corresponding insoluble polymer-bound

5   ligands both in reactivity and selectivity in AD
reactions. In addition, these chiral homopolymers
provide the same enantioselectivity and reactivity as
free ligands in solution. Furthermore, the polymer
serves as a scaffold allowing simple product separation,

10   polymer-bound ligand recovery, and recycling of the
chiral liquid phase support without a loss of catalytic
activity.

One aspect of the invention is directed to a PEG

15   bound alkaloid ligand. This PEG bound alkaloid ligand
includes a polyethylene glycol which is soluble in
aqueous medium and precipitable in aqueous/ether medium,
and an alkaloid ligand coupled to the polyethylene
glycol. Preferred alkaloid ligands are selected from

20   the following group, viz.:
            1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
            1,4-bis-(9'-O-quinidyl)-phthalazine;
            3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
            3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-

25   (9'-O-dihydroquinyl)-phthalazine;
            1,4-bis-(9'-O-quinyl)-phthalazine;
            3,6-bis-(9'-O-dihydroquinyl)-pyridazine;
            3,6-bis-(9'-O-quinyl)-pyridazine;
            dimethylcarbamoyl dihydroquinidine;

30   benzoyl dihydroquinidine;
            4-methoxybenzoyl dihydroquinidine;
            4-chlorobenzoyl dihydroquinidine;
            2-chlorobenzoyl dihydroquinidine;
            4-nitrobenzoyl dihydroquinidine;

35   3-chlorobenzoyl dihydroquinidine;
            2-methoxybenzoyl dihydroquinidine;
            3-methoxybenzoyl dihydroquinidine;

SUBSTITUTE SHEET (RULE 26)

- 7 -

2-naphthoyl-dihydroquinidine;
cyclohexanoyl dihydroquinidine;
*p*-phenylbenzoyl dihydroquinidine;
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinine;
4-methoxybenzoyl dihydroquinine;
4-chlorobenzoyl dihydroquinine;
2-chlorobenzoyl dihydroquinine;
4-nitrobenzoyl dihydroquinine;
3-chlorobenzoyl dihydroquinine;
2-methoxybenzoyl dihydroquinine;
3-methoxybenzoyl dihydroquinine;
2-naphthoyl dihydroquinine;
cyclohexanoyl dihydroquinine;
p-phenylbenzoyl dihydroiquinone;
acrylonitrile co-polymer of 9-(4-
chlorobenoyloxy)-quinidine;
acrylonitrile co-polymer of 11-((2-
acryloyloxy)ethyl-sulfinyl)-9-(4-
chlorobenoyloxy)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 11-[2-
acryloyloxy)ethylsulfonyl]-9-(N,N-
dimethylcarbamoyl)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 9-(10-undecanoyl)-
10,11-dihydroquinidine; and
alkaloid ligands represented by the following
structures:

- 8 -

and

In a preferred embodiment, the above alkaloid
ligands are coupled to said polyethylene glycol by a
5   linkage selected from the group consisting of ester
linkage, amide linkage, thoester linkage, ester linkage,
thiether linkage, and sulphone linkage. Preferred
examples of the PEG bound alkaloid ligand are
represented by the following structures:

10

SUBSTITUTE SHEET (RULE 26)
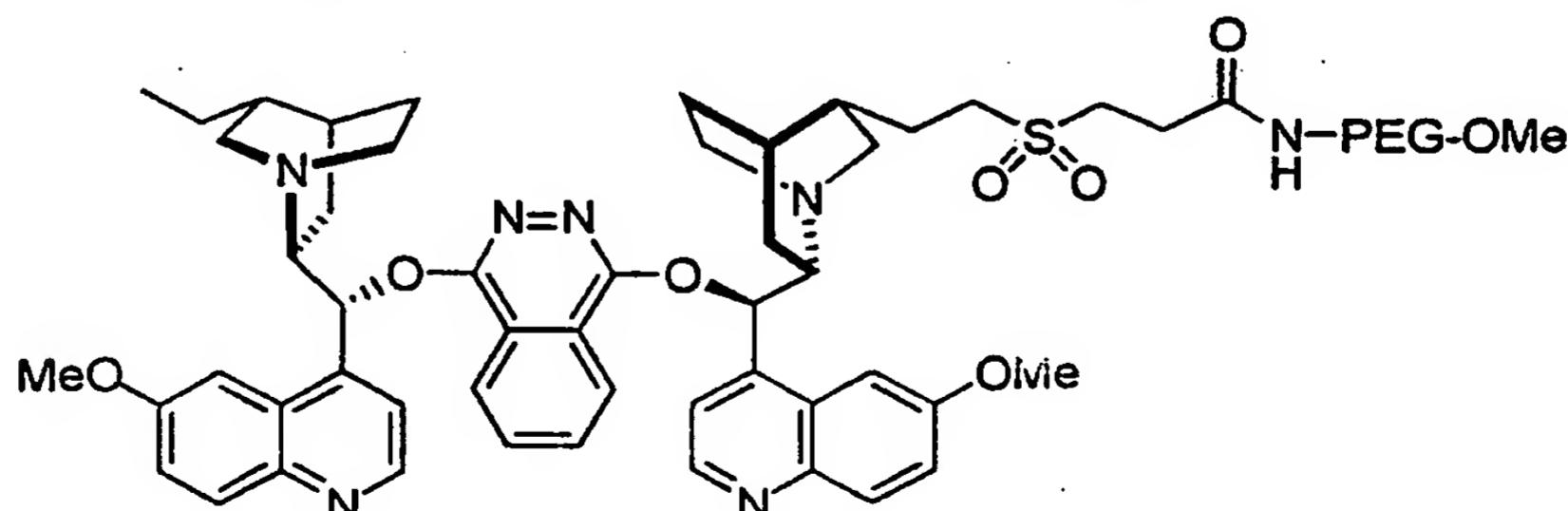
- 9 -

,
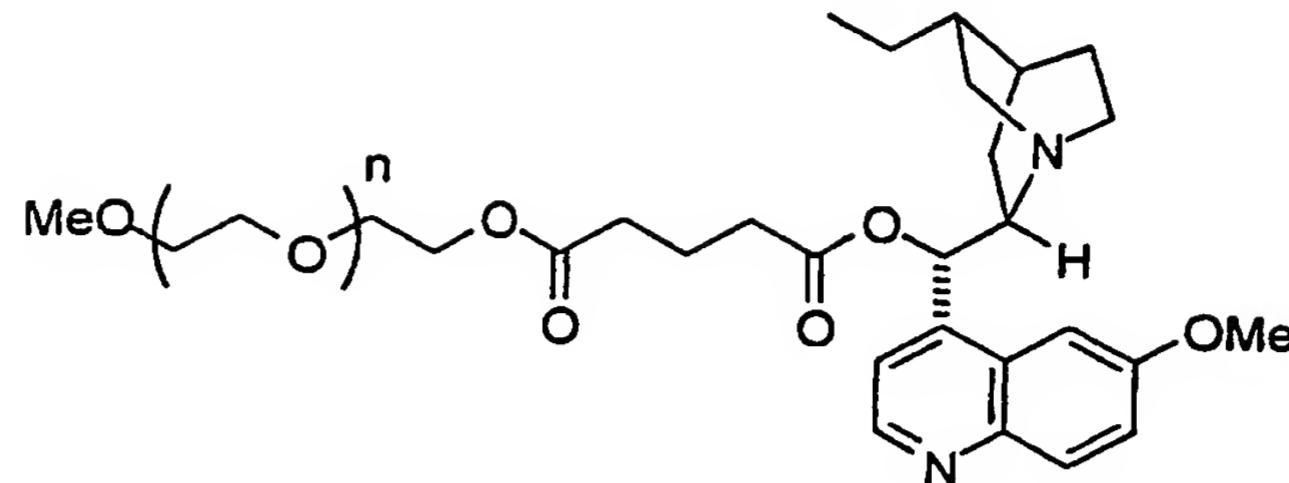
and
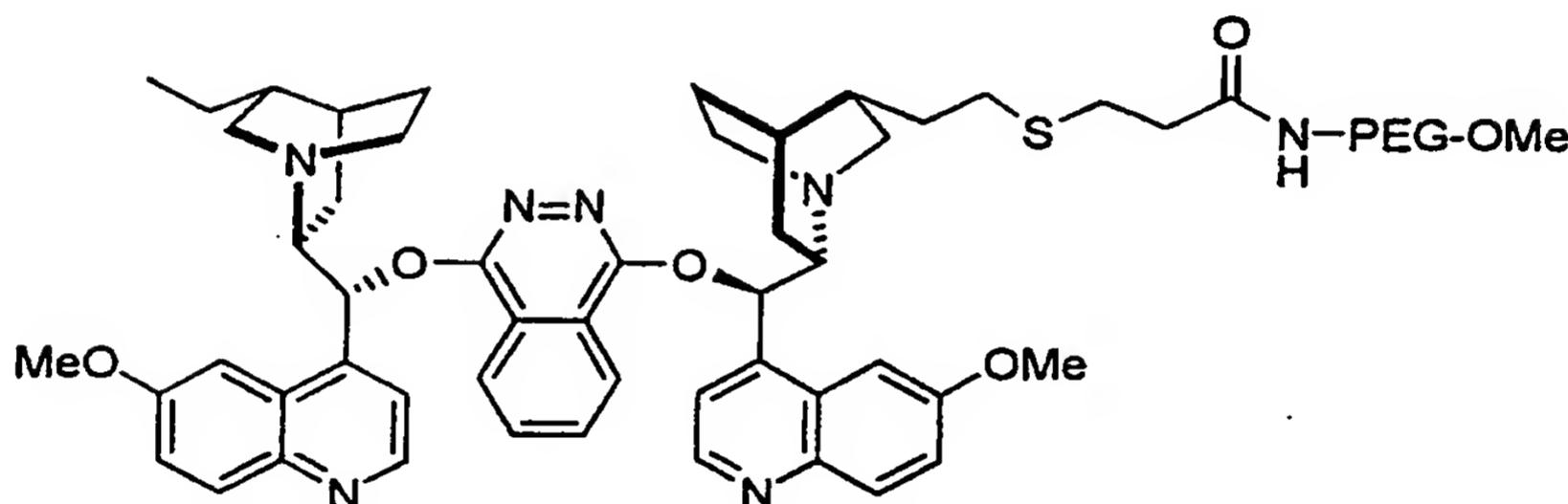
Another aspect of the invetnion is directed to an
improved process for catalyzing a hydroxylation
reaction. The process is of the type which includes a
step for admixing, within a reaction medium, an olefin,
an oxidizing agent, a catalyst for catalyzing the
hydroxylation reaction, and an alkaloid ligand for
accelerating the catalysis of the hydroxylation
reaction. The process is improved by the use of a PEG
bound alkaloid ligand. The PEG bound alkaloid ligand is
soluble in the reaction medium and precipitable in a
precipitation medium. In a preferred embodiment, the
hydroxylation reactions are asymmetric dihydroxylation
reaction and the PEG bound alkaloid ligand is chiral. A
preferred oxidizing agent is a mixture which includes
$K_3Fe(CN)_6$ (potassium ferricyanide III), $CH_3SO_2NH_2$

SUBSTITUTE SHEET (RULE 26)

- 10 -

(methanesulfonamide), OsO$_4$ and K$_2$CO$_3$ (potassium
carbonate). Another preferred oxidizing agent is a
mixture which includes methylmorpholine *N*-oxide (NMO),
tetraethylammonium acetate tetrahydrate, and OsO$_4$. The
preferred catalyst is OsO$_4$. Preferred reaction media are
acetone/water or butanol/water. Preferred precipitation
media include the addition of diethyl ether or cold
ethanol to the reaction media.

Another aspect of the invention is directed to a
process for catalyzing an hydroxylation reaction. In
the first step of this process, an olefin, an oxidizing
agent, a catalyst for catalyzing the hydroxylation
reaction, and an alkaloid ligand for accelerating the
catalysis of the hydroxylation reaction are admixed in a
reaction medium. The admixture occurs in a reaction
medium under reaction conditions for producing an
hydroxylation product. In the second step, a
precipitation medium is admixed with the reaction medium
of the first step for precipitating the PEG bound
alkaloid ligand. In the third step, the precipitated
PEG bound alkaloid ligand of the second step is
separated from the hydroxylation product so as to
recover the PEG bound alkaloid ligand. In a preferred
mode, the hydroxylation reaction in the first step is an
asymmetric dihydroxylation reaction and the PEG bound
alkaloid ligand is chiral.

Another aspect of the invention is directed to a
further process for catalyzing an hydroxylation
reaction. In the first step of this process, one or
more reactants are admixed with a catalyst for
catalyzing the hydroxylation reaction and with a PEG
bound alkaloid ligand for accelerating the catalysis of
the hydroxylation reaction. The admixture occurs occurs
in a reaction medium under reaction conditions for
producing an hydroxylation product, In the second step,

SUBSTITUTE SHEET (RULE 26)

a precipitation medium is admixed the reaction medium of
of the first step for precipitating the PEG bound
alkaloid ligand. In the third step, the hydroxylation
product of the second step is separated B from the
precipitated PEG bound alkaloid ligand for obtaing
purified product. In a preferred mode, the
hydroxylation reaction is an asymmetric dihydroxylation
reaction and the PEG bound alkaloid ligand is chiral.

Brief Description of Figures:

Figure 1 illustrates a prior art alkaloid ligand,
i.e. compound **1**, a PEG radical, i.e., compound **4**,
alkaloid ligand coupled to a linkage unit, i.e. compound
3, and a PEG bound alkaloid ligand, i.e., compound **2**.

Figure 2 illustrates the synthesis of ligands **2** and
3 with the following conditions: (a) TEA, DMAP, glutaric
anhydride (60 %); (b) DCC, DMAP, ROH (95 %).

Figure 3 illustrates the comparison of catalytic
asymmetric hydroxylations using compound **1-4**. The
indicated notations are as follows: (a) see Petri et al.
Chirality **1995**, 7, 580 for experimental details; (b)
results from Petri et al. *Chirality* **1995**, 7, 580; ligand
2, which was recovered from entry 3, was recycled a
total of four times; (d) for the purpose of comparison,
the reaction was stopped after 5 hours (e) slow addition
time of olefin.

Figure 4 illustrates polymer-bound *trans*-cinnamate
esters **7-11** for the Sharpless AD reaction.

Figure 5 illustrates the reaction in which trans-
cinnamic acid was immobilized to the four polymeric
supports **7-11** (figure 4) and the reactivity of **7-11** was

- 12 -

demonstrated by using the ligands **13** and **14** for the
Sharpless AD reaction.

Figure 6 tabulates various AD reactions conducted
upon various polymer bound *trans*-cinnamate esters using
the ligands **13** and **14**. The indicated notations are as
follows: [a] OsO$_4$ equivalents realtive to olefin.
[ligand]/[OsO$_4$] = 2.5. [b] Method A: K$_3$Fe(CN)$_6$ and *t*-
butanol/water = 1/1 system at room temperature. Method
B: *N*-methylmorpholine-*N*-oxide and acetone/water = 10/1
system at 4°C. [c] Determined from the ratio of diol
proton signals to the remaining olefin signals by NMR.
[d] Determined through NMR analysis of the derived *bis*-
Mosher ester of the diol.

Figure 7 illustrates the chemical synthesis of
ligands **20** and **14**.

Figure 8 tabulates various catalytic Asymmetric
Dihydroxylation Reactions using Ligand **14**. The
indicated notations are as follows: (a) For NMO system,
the molar ratio of olefin/OsO$_4$/ligand = 1/0.04/0.1, and
for K$_3$Fe(CN)$_6$ system, the molar ratio was 1/0.005/0.1.
(b) Number in parenthesis represents results for a free
ligand (DHQD)$_2$PHAL from Sharpless et al. *J. Org. Chem.*
1992, *57*, 2768.

- 13 -

Detailed Description of the Invention

The invention is directed to the synthesis and use of polyethylene glycol monomethyl ether-bound cinchona alkaloid ligands in the ligand-accelerated catalytic (LAC) Sharpless asymmetric dihydroxylation reaction (AD) with a range of olefins.

Example 1. Synthesis and Exemplary use of Polyethylene glycol monomethyl ether-bound cinchona alkaloid ligands in the AD reaction

The following examples are exemplary conditions which demonstrate the versatility of the methodology and are not meant to be restrictive with the models disclosed. Rather, the methodology can be used with symmetrical, nonsymmetrical, substituted and unsubstituted - primary, secondary or tertiary olefins. In addition, other commercially available alkaloid ligands can be used in lieu of the disclosed dihydroquinidine hydrochloride 5 (Figure 2). Preferred alkaloid ligands include the following:

1. from U.S. Patent No. 5,260,461, incorporated herein by reference:
   1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
   1,4-bis-(9'-O-quinidyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
   3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-(9'-O-dihydroquinyl)-phthalazine;
   1,4-bis-(9'-O-quinyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinyl)-pyridazine;
   3,6-bis-(9'-O-quinyl)-pyridazine;
2. from U.S. Patent No. 4,871,855, incorporated herein by reference:
   dimethylcarbamoyl dihydroquinidine;
   benzoyl dihydroquinidine;
   4-methoxybenzoyl dihydroquinidine;

- 14 -

4-chlorobenzoyl dihydroquinidine;
2-chlorobenzoyl dihydroquinidine;
4-nitrobenzoyl dihydroquinidine;
3-chlorobenzoyl dihydroquinidine;
5   2-methoxybenzoyl dihydroquinidine;
3-methoxybenzoyl dihydroquinidine;
2-naphthoyl-dihydroquinidine;
cyclohexanoyl dihydroquinidine;
p-phenylbenzoyl dihydroquinidine;
10   dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinine;
4-methoxybenzoyl dihydroquinine;
4-chlorobenzoyl dihydroquinine;
2-chlorobenzoyl dihydroquinine;
15   4-nitrobenzoyl dihydroquinine;
3-chlorobenzoyl dihydroquinine;
2-methoxybenzoyl dihydroquinine;
3-methoxybenzoyl dihydroquinine;
2-naphthoyl dihydroquinine;
20   cyclohexanoyl dihydroquinine;
p-phenylbenzoyl dihydroiquinone;

3. From U.S. Patent No. 5,126,494, incorporated herein
by reference:
acrylonitrile co-polymer of 9-(4-
25   chlorobenoyloxy)-quinidine;
acrylonitrile co-polymer of 11-((2-
acryloyloxy)ethyl-sulfinyl)-9-(4-
chlorobenoyloxy)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 11-[2-
30   acryloyloxy)ethylsulfonyl]-9-(N,N-
dimethylcarbamoyl)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 9-(10-undecanoyl)-
10,11-dihydroquinidine; and
alkaloid ligands represented by the following
35   structures:

SUBSTITUTE SHEET (RULE 26)

- 15 -
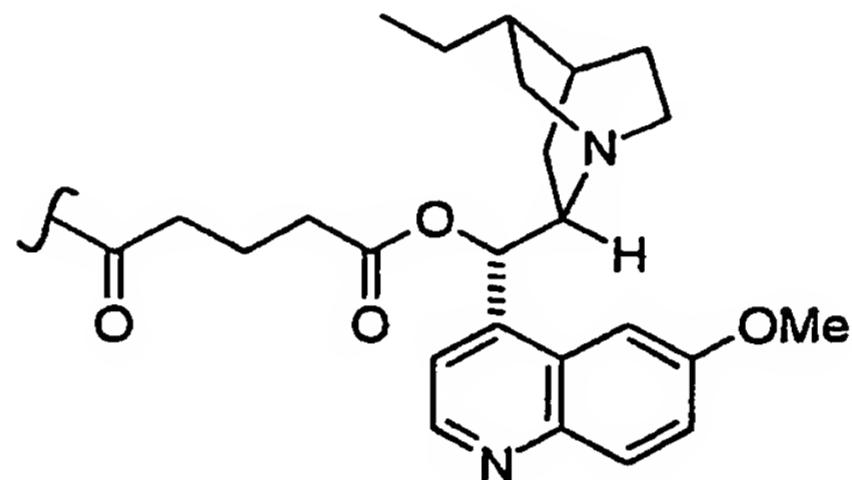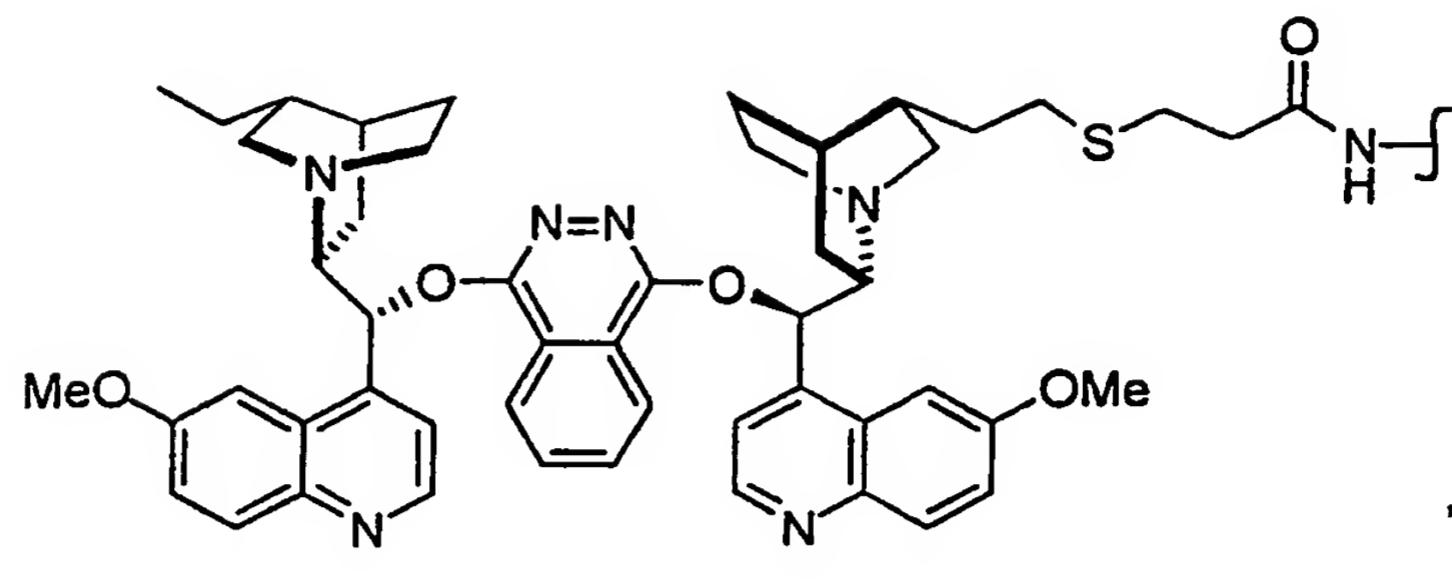
and
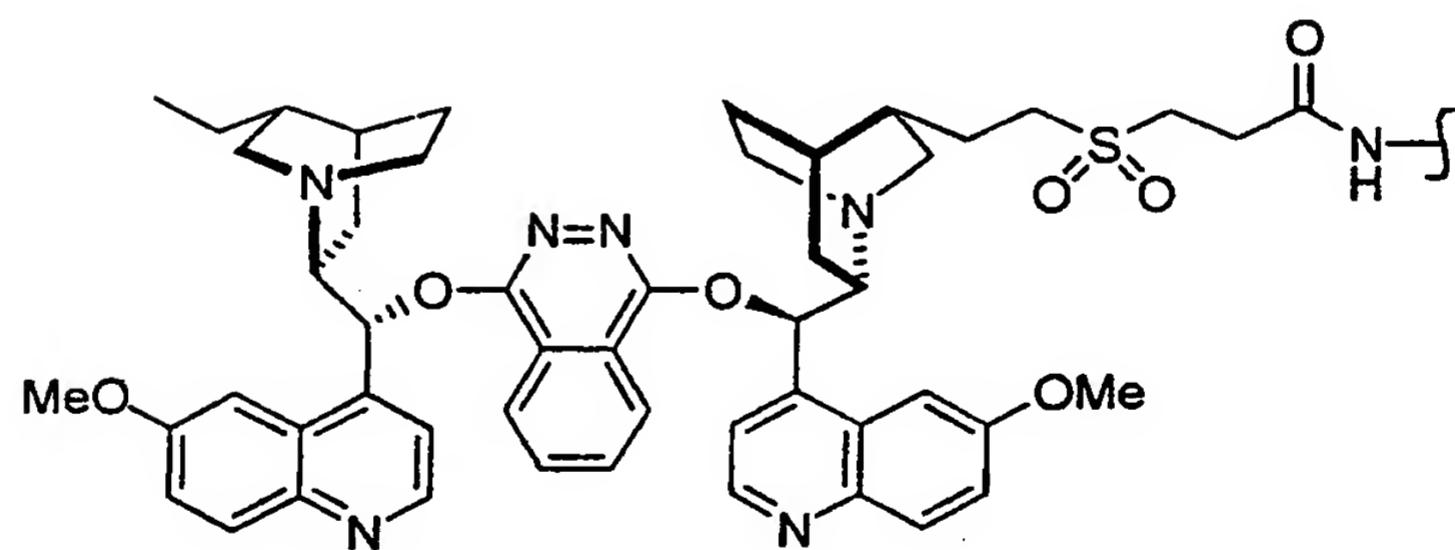
Reaction conditions which cover temperature,
5   substrate equivalents, reaction time(s), work-up(s) and
buffer solutions (pH levels) may vary, depending on the
substrate used, however all proportions are
approximately the same.   A representative procedure is

SUBSTITUTE SHEET (RULE 26)

- 16 -

provided in the synthetic protocals.

In an effort to circumvent the problems observed
with insoluble supports and LAC, yet, provide the
5   economical and physical advantages (product isolation
and reagent recovery) that a polymeric support can
offer, we have developed the soluble homopolymer MeO-PEG
as a suitable scaffold for the AD reaction. The
synthesis of polyethylene glycol monomethyl ether bound
10   cinchona alkaloid ligands (Figure 1) and their
successful use in the LAC asymmetric dihydoxylation
reaction of various olefins is described as follows.

The synthesis of the MeO-PEG-bound dihydroquinidine
15   ligands is depicted in Figure 2. The commercially
available hydroquinidine 5 (Aldrich) was acylated using
glutaric anhydride and 4-N,N'-dimethylaminopyridine
(DMAP) to provide carboxylic acid 6. This reaction,
though simple, provides the linking unit necessary for
20   attachment to the homopolymer MeO-PEG or any other amino
or alcohol group. The coupling of acid 6 to
polyethylene glycol monomethyl ether and ethyl alcohol
in the presence of dicyclohexylcarbodiimide and DMAP
produced the homopolymer 2 and its simple diester
25   homologue 3 respectively.

The chiral homopolymer 2 was the archetype used to
examine and compare all of the AD reactions
investigated. The structural similaritiy of 2 to the
30   insoluble acrylonitrile ligand 1, allowed for a direct
comparison between soluble and insoluble supports to be
made (Kim et al. Tetrahedron Lett. 1990, 31, 3003) while
contrasting the reactivity of ligands 2, 3, and 4 in the
AD reaction would delineate any effect that the
35   polyethylene glycol backbone may have on asymmetric
induction. In addition, to standardize the comparisons
between our soluble ligand support and the insoluble

ligand support, we us d the same conditions as reported
for the ligand 1- AD catalytic reaction (Kim et. al.
Tetrahedron Lett. 1990, 31, 3003).

5   The MeO-PEG-supported catalyst 2 is completely
soluble in an acetone-water mixture (v/v = 9/1); thus
the catalytic reaction is completely homogeneous. Of
greater note is that the reaction is complete within the
same time frame as that of its solution counterpart with
10   no decrease of yields or enantioselectivity as
tablutated in Figure 3. For this methodology to be
useful, product isolation, separation, and recovery of
the polymer bound ligand must be straightforward and
reliable. Upon completion of the AD reaction, the
15   entire mixture was diluted with methylene chloride,
dried (anhydrous sodium sulfate) and filtered. Diethyl
ether was added to the resulting mixture in order to
precipitate MeO-PEG-bound ligand (typically, the MeO-
PEG-bound ligand was recovered in >98 % yield). The
20   filtrate contained the dihydroxylated product.

         The asymmetric dihydroxylation of a variety olefins
by ligands 1-4 is shown in Figure 3. Immediately
evident is the fact that MeO-PEG-bound ligand 2 is more
25   efficient than the insoluble polymer bound ligand 1 (Kim
et. al. Tetrahedron Lett. 1990, 31, 3003), both in its
enantioselectivity and reactivity (entries 1 and 2 ,
Figure 3). What is more, the polymer-bound ligand 2 is
easily recovered in near quantitative fashion and
30   recycled several times with no loss of reaction yield or
enantioselectivity (entry 3, Figure 3). With all four
olefins tested, MeO-PEG-bound ligand 2 was as effective
as free ligand 3 (compare entries 2 and 4, entries 6 and
7, entries 8 and 9, and entries 10 and 11). These
35   findings strongly suggest that the MeO-PEG back-bone
does not influence or affect the observ d asymmetric
induction (entry 5). Furthermore, these findings

SUBSTITUTE SHEET (RULE 26)

- 18 -

provide direct support for our notion that for successful polymer-bound LAC all components involved in the reaction must be able to interact freely with each other in solution.

5

In summary, a process has been invented which demonstrates how a chiral ligand can be integrated into a soluble polymeric species so that LAC can operate in an unhindered manner on a polymer support. The soluble
10 polymer-bound ligand provides all the advantages that an insoluble support can offer, while also being as effective as a free ligand both in reactivity and selectivity. This new soluble polymer bound-ligand system should be applicable to other classes of AD
15 ligands for improved enantioselectivity (Kolb et al. Chem. Rev. 1994, 116, 2483) as well as other enantioselective catalytic processes (Takaya et al. J. Am. Chem. Soc. 1987, 109, 1596; Zhang et al. J. Am. Chem. Soc. 1990, 112, 2801; Lowenthal et al. Tetrahedron
20 Lett. 1991, 32, 7373; Li et al. J. Am. Chem. Soc. 1993, 115, 5326; Evans et al. J. Am. Chem. Soc. 1993, 115, 5328; Johnson et al. in Catalytic Asymmetric Synthesis Ed.; VCH: Weinheim, 1993; pp. 103-158; Jacobsen et al. in Catalytic Asymmetric Synthesis; Ojima, I. Ed.; VCH:
25 Weinheim, 1993; pp. 159-202; Li et al. Angew. Chem., Int. Ed. Engl. 1996, 35, 451).

The MeO-PEG polymer will not only be useful to the research chemist but also for effecting the separation
30 of catalyst from product in homogeneous industrial applications (Steckhan et al. Angew. Chem. Int. Ed. Engl. 1990, 29, 388; Herrmann et al. Angew. Chem. Int. Ed. Engl. 1993, 32, 1524; Bergbreiter et al. J. Am. Chem. Soc. 1993, 115, 9295; Horvath et al. Science 1994,
35 266, 72). Finally because of its desirable physical properties, this and other ligand accelerated catalysts that are incorporated within liquid phase supports may

find use in automated high through-put synthetic efforts
(Frisbee et al. J. Am. Chem. Soc. 1984, 106, 7143;
Sabadosa et al. Lab. Rob. Automation 1989, 1, 265;
Dewitt et al. Current Opin. Biotech. 1995, 6, 640).

5

Example 2. Synthesis and Exemplary use of attachment of small organic olefinic moiety to various polymeric matrixs with the Sharpless AD reaction

10   Since the initial discovery of Merrifield
(Merrifield et al. J. Am. Chem. Soc. 1963. 85. 2149-
2154) concerning the synthesis of oligopeptides the use
of polymers as supports, reagents or even catalysts, for
various syntheses mostly related to fine chemistry has
15   increased (Crowley et al. Acc. Chem. Res. 1976, 9, 135-
144; Leznoff et al. Acc. Chem. Res. 1978, 11, 327-333;
Manecke et al. Angew. Chem. Int. Ed. Engl. 1978, 17,
657-670; Frechet Tetrahedron 1981, 37, 663-688).
Recently, a high level of activity has been devoted to
20   the field due to the application of combinatorics to the
drug discovery arena (Molecular Diversity and
Combinatorial Chemistry (eds.: I.M. Chaiken and K.D.
Janda) American Chemical Society, Washington, D.C.,
1996; Fruchtel et al. Angew. Chem. Int. ed. Engl. 1996,
25   35, 17-42; Balkenhohl et al. Angew. Chem. Int. ed.
Engl. 1996, 35, 2288-2337). Although a resurgence of
interest in polymers for organic synthesis has been
seen, little effort has been paid to the structural
parameters of the supports. This being most evident in
30   the realm of automation of organic synthesis.

In an effort to delineate the shortcomings of
insoluble polymer bound ligand-accelerated catalysis
(LAC), we show how a chiral ligand can be integrated
35   onto a soluble polymeric species so that LAC can operate
in an unhindered manner on a polymer support (Han et al.
J. Am. Chem. Soc. 1996, 118, 7632-7633). However, the

converse wherein a small organic moiety is attached to a
polymeric matrix and the polymer's influence on the LAC
reaction has yet to be investigated. Implications from
the successful combination of these two scenario's being

5   that a multipolymer LAC reaction maybe a feasiable
target. In this context, we have collected data using
both solid and liquid phase polymers to evaluate the
influence of the support structure on the Sharpless
asymmetric dihydroxylation (AD) reaction. The outgrowth

10   of these findings have allowed us to successfully run a
multipolymer Sharpless AD reaction.

A variety of supports have been recently engaged in
organic synthesis (Terrett et al. *Tetrahedron* **1995**, 51,

15   8135-8173; Thompson et al. *Chem. Rev.* **1996**, 555-600;
Hermkens et al. *Tetrahedron* **1996**, 52, 4527-4554).
Typically, they may be grouped into three categories.
(1) Minimal cross-linked supports that form well
solvated gels (R.B. Merrifield, *Angew. Chem. Int. Ed.*

20   *Engl.* **1985**, 24, 799-810); (2) Porous but rigid supports
with a high degree of cross linking (Bartholin et al.
Prog. Polym. Sci. **1982**, 8, 277-332); (3) Linear soluble
polymers also known as liquid phase supports (Geckeler
et al. in *Advances in Polymer Science*, Vol. 121 (Eds.

25   Spring-Verlag, Berlin, 1995, p. 31; Bayer et al. ,
Angew. Chem. Int. Ed. Engl. **1991**, 30, 113-129;
Bergbreiter in *Proceedings of the Sixth Annual IUCCP
Symposium on Functional Polymers.* (Eds. D.E. Bergbreiter
and C.R. Martin) Plenum Press, New York, 1989, p. 143.

30   Two low divinyl benzene-cross-linked polystyrene beads
(Merrifield and Wang resin) and the graft copolymer
polystyrene-polyethylene glycol (Tentagel) were utilized
as category-1 supports. The choice of these resins was
based on their fundamental differences. Merrifield and

35   Wang resins are relatively hydrophobic matrices while
Tentagel is considered to be a hydrophilic tentacle
polymer with more "solution-like" characteristics. The

- 21 -

category-3 support used was polyethylene glycol (PEG).
Besides it fulfilling the criteria of a group-3 polymer,
this homopolymer was enlisted as it contrasted the
chemical reactivity differences between PEG and
5   Tentagel.

Trans-cinnamic acid was immobilized to the four
polymeric supports (Figure 4). Using this format
insured that all supports would have an olefin tethered
10   as an ester with the composition of the polymer
determining the overall reactivity. Furthermore,
because the reactivity of ethyl trans-cinnamate (11) is
a documented substrate for the AD reaction using the
ligand 1,4-phthalazinediyldiether hydroquinidine
15   [(DHQD)₂PHAL, 14, Figure 5] Sharpless et al. Org. Chem.
1992, 57, 2768-2771, a direct correlation could be made
between solution and polymeric reactions.

Figure 6 shows that the resins structural make-up
20   is the dominant factor influencing the AD reaction.
Overall the amount of metal/ligand used, reaction time
required for product conversion, and enantiomeric excess
observed varies greatly depending on the support.
Contrasting all four polymeric supports in terms of the
25   AD reaction clearly shows that the non-cross-linked
liquid phase resin 10 (entries 6 and 10; Figure 6)
provides the best overall results when considering
reaction time, conversion percent, enantiomeric excess
and metal/ligand ratio. Furthermore, this soluble
30   polymer substrate compares favorably with entry 11 which
details our findings for the matrix removed olefin
counterpart 11.

Specifically looking at the three insoluble
35   supports Tentagel-9 out performed the Wang-8 and
Merrifield-7 resins in the optimum enantioselective
oxident, potassium ferricyanide (entries 1-5). However,

SUBSTITUTE SHEET (RULE 26)

the cross-linked polystyr ne suppports-8/9, can provide
a suitable environment for LAC when NMO is applied as
the oxident and acetone/water is the solvent (entries 7
and 8). It may have been anticipated that supports 7

5   and 8 would show an overall inability to support the AD
reaction in the potassium ferricyanide oxident system as
these polymers have rather modest swelling properties in
the solvent system employed. The consequences of poor
swelling would include limited chain mobility which

10   could compromise the location and distribution of
catalyst to olefin within these matrices.

Somewhat unexpected was the large amount of metal
and ligand that was required for the Tentagel resin-9 to

15   provide a respectable reaction time, conversion and
enantioselec-tivity (compare entries 3,4, and 5).
Interestingly there appears to be a threshold of
catalyst that is required with Tentagel for any
conversion to diol be seen (compare entries 3 and 4).

20   We investigated this aspect further through the
following two experiments. In one reaction conditions
as detailed in entry 4 were utilized. After 24h fresh
unbound olefin 11 (0.125 mmol.) was added to the
reaction mixture as was OsO_4 (0.02 eq.relative to the

25   olefin), K_2CO_3 (3.0 eq relative to the olefin), and
$K_3Fe(CN)_6$ (3.0 eq relative to the olefin). The reaction
mixture was analyzed after 10h and was found to have
only obtained 10% conversion of 11 to 12b. In the
second reaction unbound olefin 11 was used throughout

30   the same sequence of events, however, in this scenario
recharging the reaction mixture with 11 provided
complete conversion to 12b in 2.5h. Such results suggest
that free ligand becomes entangled in the insoluble
support limiting its availability. Thus, while resin-9

35   is a more hydrophilic copolymer than resins-7 and 8 it
still must be considered a "quasi-homgeneous" matrix
which is subject to some of the same limitations found

- 23 -

within insoluble resins.

    In our defining of the influence of the structure
and support texture on the kinetics and
enantioselectivty of the AD reaction (vide supra) we
identified that a correct combination of soluble and
insoluble polymers (i.e. a multipolymeric reaction)
could in principle make a tenable AD process. The use
of more than a single polymeric reagent/catalyst in
reactions either simultaneously or consecutively has
been accomplished, but its exploitation has been limited
to date (Examples in the area of peptide syntheses
include: a) G. Heusel, G. Bovermann, W. Göhring, G.
Jung, *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 642-643. b)
H. Frank, H. Hagenmaier, *Experentia* **1975**, 31, 131-133.
For examples other than peptides see: a) B.J. Cohen,
M.A. Kraus, A. Patchornik, *J. Am. Chem. Soc.* **1977**, 99,
4165-4167. b) C.V. Pittman, L.R. Smith, *J. Am. Chem.
Soc.* **1975**, 97, 1749-1754 c) J.P. Collman, K.M. Kosydar,
M. Bressan, W. Lamanna, T. Garrett, *J. Am. Chem. Soc.*
1984, 106, 2569-2579. d) D.E. Bergbreiter, R. chandran,
J. Am. Chem. Soc. **1987**, 109, 174-179. e) D. E.
Bergbreiter, R. Chandran, *J. Am. Chem. Soc* **1985**, 107,
4792-4793. f) J. J. Parlow, *Tet. Lett.* **1995**, 36, 1395-
1396. g) F. Svec, J. M. J. Frechet, *Science* **1996**, 273,
205-211. For the detection of highly reactive
intermediates using two polymeric reagents simultaneous
"Three phase text", see J. Rebek *Tetrahedron*, **1979**, 35,
723-731 and references cited therein). The combination
of Tentagel resin-9 and MeO-PEG-[(DHQD)$_2$PHAL] **14**, (Figure
5) was investigated as the multipolymer components.
Entry 12 shows that this combination of polymers can
successfully support LAC. These two polymers are
physically quite different, yet, the outgrowth of this
methodology translates into facile product separation
and ligand re-isolation. The significance of such
technology should have direct application to the

- 24 -

automation of synthetic processes (Frisbee et al. *J. Am. Chem. Soc.* **1984**, 106, 7143-7145. b) Dewitt et al. *Curr. Biol.*, **1995**, 6, 640-645. c) Kramer et al. *Chemtech* **1989**, 19, 682-688. d) Hobbs Dewitt et al. *Acc. Chem. Res.* **1996**, 29, 114-122).

From the literature (Terrett et al. *Tetrahedron* **1995**, 51, 8135-8173; Thompson et al. *Chem. Rev.* **1996**, 555-600; Hermkens et al. *Tetrahedron* **1996**, 52, 4527-4554) as well as from the results reported here a few guidelines seem to be emerging concerning the influence of the structure and support texture on the kinetics and selectivity of polymer supported organic reactions. These lines appear valid for both supported catalysts as well as for organic moieties attached to these matrices. The key in the context of both systems can be assimilated back to properties inherent to all polymers: Accessibility or lack of, and microenvironment, the latter often being a prerequisite for the first.

In the field of small molecule combinatorics example 2 demonstrates that multipolymeric reactions should be applicable in the automation of organic synthesis.

Example 3: PEG Approach to the Sharpless Catalytic Asymmetric Dihydroxylation (AD) using a [(DHQD)2PHAL-PEG-OMe] Ligand.

In an effort to circumvent the problems associated with heterogeneous reactions, we illustrate in example 1 (vida supra) a homogeneous extention to the AD reaction using a soluble polymer, poly(ethylene glycol) mono-methyl ether (MeO-PEG), bound cinchona alkaloid ligand (Han et al. *J. Am. Chem. Soc.* **1996**, *118*, 7633). This liquid-phase methodology (Han et al. *J. Am. Chem. Soc.* **1996**, *118*, 2539; Han et al. *Methods in Enzymology* **1996**, *267*, 234; Han et al. *Proc. Natl. Acad. Sci. USA* **1995**,

92, 6419) provided all of the advantages that an
insoluble polymer has to offer, while also being as
effective as the free ligand in terms of both reactivity
and enantioselectivity. However, the ligand **5** (Figure
2) utilized was not the most effective in terms of
enantioselectivity and reactivity for the solution-phase
AD reaction. Therefore in an attempt to improve our
liquid-phase approach to the AD reaction we illustrate
in this example the synthesis of a (DHQD)$_2$PHAL ligand
bound to MeO-PEG-NH2 and its successful use in the AD
reaction of various olefins (Figures 7 and 8).
Furthermore, we extend the methodology to include
additional ligands which, when bound to the PEG polymer,
afford successful use in the AD reaction. The
additional ligands include the following alkaloid
ligands:
> 1. from U.S. Patent No. 5,260,461, incorporated herein
>   by reference:
>> 1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
>> 1,4-bis-(9'-O-quinidyl)-phthalazine;
>> 3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
>> 3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-
>> (9'-O-dihydroquinyl)-phthalazine;
>> 1,4-bis-(9'-O-quinyl)-phthalazine;
>> 3,6-bis-(9'-O-dihydroquinyl)-pyridazine;
>> 3,6-bis-(9'-O-quinyl)-pyridazine;
> 2. from U.S. Patent No. 4,871,855, incorporated herein
>   by reference:
>> dimethylcarbamoyl dihydroquinidine;
>> benzoyl dihydroquinidine;
>> 4-methoxybenzoyl dihydroquinidine;
>> 4-chlorobenzoyl dihydroquinidine;
>> 2-chlorobenzoyl dihydroquinidine;
>> 4-nitrobenzoyl dihydroquinidine;
>> 3-chlorobenzoyl dihydroquinidine;
>> 2-methoxybenzoyl dihydroquinidine;
>> 3-methoxybenzoyl dihydroquinidine;

SUBSTITUTE SHEET (RULE 26)

2-naphthoyl-dihydroquinidine;

cyclohexanoyl dihydroquinidine;

p-phenylbenzoyl dihydroquinidine;

dimethylcarbamoyl dihydroquinidine;

5   benzoyl dihydroquinine;

4-methoxybenzoyl dihydroquinine;

4-chlorobenzoyl dihydroquinine;

2-chlorobenzoyl dihydroquinine;

4-nitrobenzoyl dihydroquinine;

10   3-chlorobenzoyl dihydroquinine;

2-methoxybenzoyl dihydroquinine;

3-methoxybenzoyl dihydroquinine;

2-naphthoyl dihydroquinine;

cyclohexanoyl dihydroquinine;

15   *p*-phenylbenzoyl dihydroiquinone;

3. From U.S. Patent No. 5,126,494, incorporated herein
   by reference:

acrylonitrile co-polymer of 9-(4-
chlorobenoyloxy)-quinidine;

20   acrylonitrile co-polymer of 11-((2-
acryloyloxy)ethyl-sulfinyl)-9-(4-
chlorobenoyloxy)-10,11-dihydroquinidine;

acrylonitrile co-polymer of 11-[2-
acryloyloxy)ethylsulfonyl]-9-(N,N-

25   dimethylcarbamoyl)-10,11-dihydroquinidine;

acrylonitrile co-polymer of 9-(10-undecanoyl)-
10,11-dihydroquinidine; and

alkaloid ligands represented by the following
structures:

30

SUBSTITUTE SHEET (RULE 26)
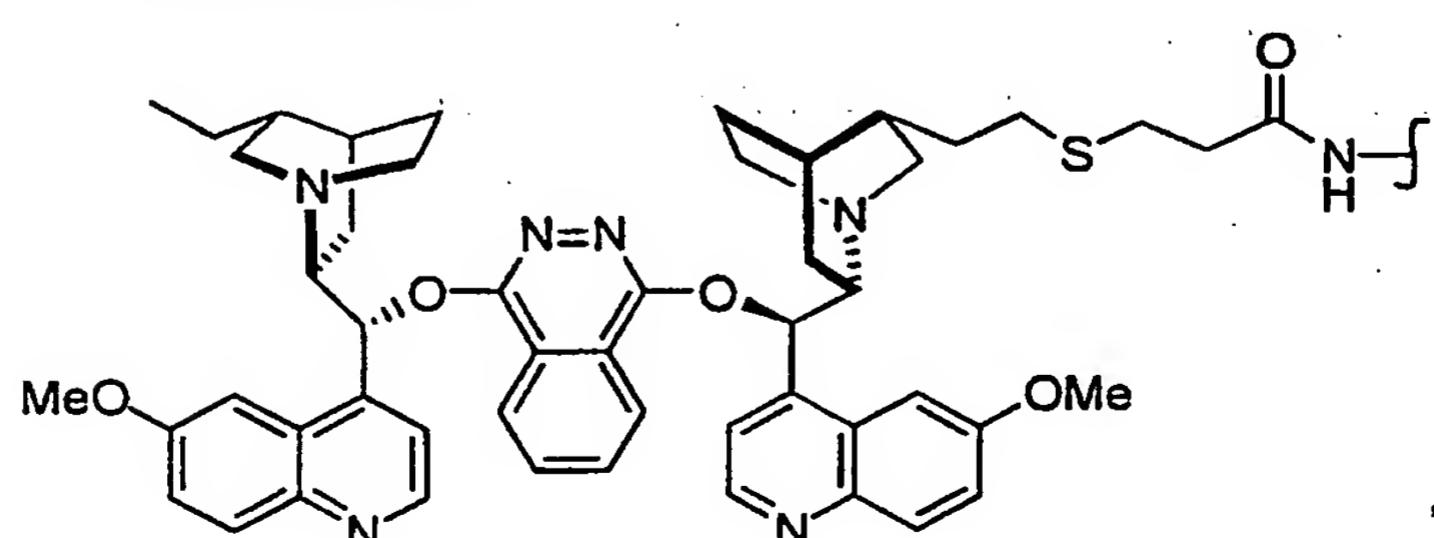
- 27 -
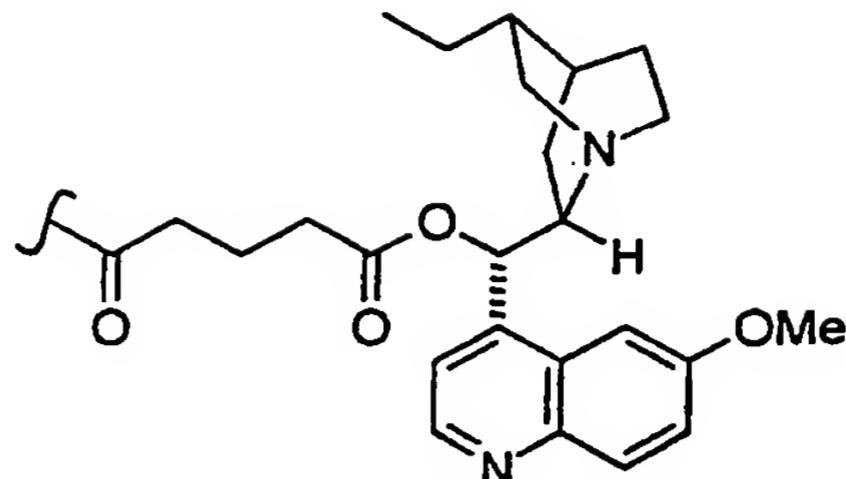
and
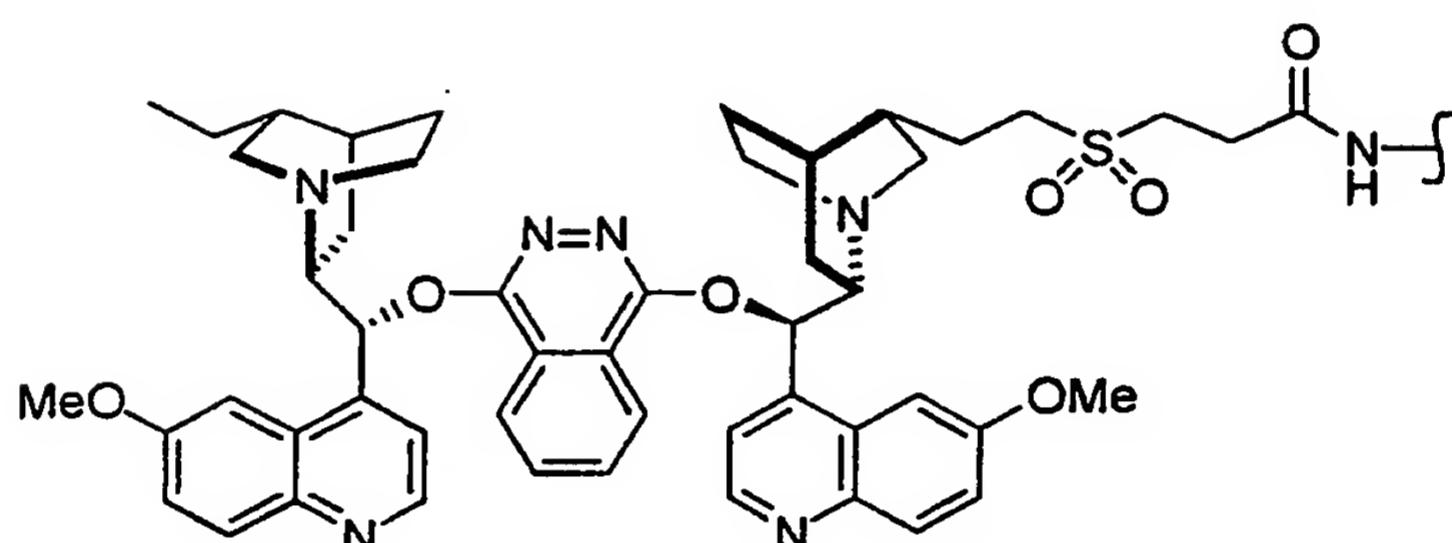
5   The five step synthetic route to **14** is outlined in
Figure 7.   In the first step, a mixture of
dihydroquinidine, 1,4-dichlorophthalazine, KOH, and K_2CO_3
in dry toluene are refluxed, with a concurrent
azeotropic removal of water, to give the mono-
10   substituted chlorophthalazine **17** which upon similar
transformation with quinidine provided the di-
substituted phthalazine **18** (Amberg et al. *J. Org. Chem.*
1993, *58*, 844; Lohray et al. *Tet. Lett.* **1994**, *35*, 6559).
The heating of **18** and 3-mercaptopropionic acid (3-MPA)
15   in the presence of 2,2'-azobisisobutyronitrile (AIBN) in
benzene (70 °C) allowed the isolation of **19** as a tan
precipitate (Inagaki et al. *Bull. Chem. Soc. Jpn.* **1987**,
60, 4121).   The acid **19** was coupled to MeO-PEG-NH2 in

SUBSTITUTE SHEET (RULE 26)

the presence of N,N- dimethylaminopyridine (DMAP) and 1,3-dicyclohexylcarbodiimide (DCC) in methylene chloride (DCM) (Pillai et al. *J. Org. Chem.* **1980**, *45*, 5364). After the reaction was complete, the insoluble urea

5   side-product was removed by filtration and the pegylated ligand **20** was isolated from the reaction mixture by precipitation following a slow addition of diethyl ether. The sulfide **20** was oxidized to the desired sulfone **14** by a mixture of OsO4/*N*-methylmorpholine-*N*-

10   oxide (NMO) [in acetone/water (v/v, 2/1)] (Kaldor et al. *Tetrahedron. Lett.* **1991**, *32*, 5043).

     Ligand **14** was completely soluble either in *t*-butanol/water or acetone/water solvent systems allowing

15   the study of homogeneous AD reactions. The AD reaction results of **14** with various olefins are shown in Figure 8 and a number of features are noteworthy. First, it is evident that the *t*-Butanol/water solvent produces considerably higher ees for all olefins tested

20   consistent with previous reports (Pini et al. *Tetrahedron Lett.* **1991**, *32*, 5175; Lohray et al. *Tetrahedron Lett.* **1992**, *33*, 5453.; Pini et al. *Tetrahedron: Asymmetry* **1993**, *4*, 2351; Lohray et al. *Tetrahedron Lett.* **1994**, *35*, 6559; Pini et al.

25   *Tetrahedron* **1994**, *50*, 11321; Pini et al. *Tetrahedron Lett.* **1995**, *36*, 1549; Sung et al. *Tetrahedron: Asymmetry* **1995**, *6*, 2687; Petri et al. *Chirality* **1995**, *7*, 580; Song et al. *Tetrahedron: Asymmetry* **1996**, *7*, 645). Second, in terms of both reaction time and

30   enantioselectivity, ligand **14** accelerated AD reactions are comparable to its free ligand counterpart, strongly suggesting that the MeO-PEG backbone does not adversely alter either asymmetric induction or the rate of formation of the osmium-ligand-olefin ternary complex.

35   Finally, the ligand **14** can be isolated in virtually quantitative yield by precipitation using diethyl ether (Han et al. *J. Am. Chem. Soc.* **1996**, *118*, 7633).

Combined with our previous example 1 (vida supra:
Han et al. *J. Am. Chem. Soc.* **1996**, *118*, 7633), the
present results demonstrate that MeO-PEG bound ligands
behave in a similar fashion to unimmoblized ligands in
5   the AD reaction. What makes this finding even more
impressive is that this soluble polymer approach
provides the added convenience of ligand recovery and
product isolation.

10   <u>Synthetic Protocals</u>
General. Methylene chloride and methanol were dried
over CaH_2 and powdered magnesium respectively.
Polyethylene glycol monomethyl ether (MeO-PEG, MW. =
5000) was purchased from Aldrich and was dried over P_2O_5
15   under vacuum before use. All other solvents and
chemicals were obtained from commercial sources, and
were used without further purification, unless otherwise
stated. NMR spectra were obtained on a Bruker AM-300
spectrometer.
20   **Synthesis of Dihydroquinidine Glutarate (Mono-ester) 6
as illustrated in Figure 2.** Dihydroquinidine
hydrochloride **5** (0.500 g, 1.38 mmol; Aldrich) dissolved
in methylene chloride was neutralized by the slow
addition of triethylamine (0.140 g, 1.38 mmol) at 4 °C.
25   This was followed by the addition of 4-(*N,N'*-
dimethyl)aminopyridine (0.170 g, 1.39 mmol) in methylene
chloride. To this reaction mixture was slowly added
glutaric anhydride (0.315 g, 2.76 mmol). The reaction
temperature was raised to room temperature, and the
30   reaction mixture was stirred for an additional 2 h. All
volatiles were removed in vacuo, and the resulting
residue was purified by column chromatography (silica-
gel, methylene chloride: methanol = 9: 1). The
dihydroquinidine glutarate (mono-ester) was obtained as
35   a white foam (0.364 g, 60.0 %): ^{1}H-NMR (300 MHz, $CDCl_3$) δ
0.95 (t, J = 7 Hz, 3H), 1.35 (m, 1H), 1.5-2.1 (m, 9H),
2.2-2.7 (m, 5H), 3.13 (q, J = 7 Hz, 1H), 3.2-3.6 (m,

3H), 4.11 (s, 3H), 7.28 (d, J = 3 Hz, 1H), 7.40 (dd, J = 9, 3 Hz, 1H), 7.43 (s, 1H), 7.72 (d, J = 4 Hz, 1H), 8.03 (d, J = 9 Hz, 1H), 8.69 (d, J = 4 Hz, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 11.8, 20.1, 21.7, 24.3, 25.5, 26.2, 34.2, 34.4, 35.9, 50.5, 51.2, 57.4, 59.3, 71.5, 102.4, 119.2, 124.2, 127.2, 131.6, 143.0, 144.8, 148.0, 160.4, 172.5, 177.3; HRMS (FAB) calcd for [C$_{25}$H$_{32}$N$_2$O$_5$ + H$^+$] 441.2389, found 441.2375.

Synthesis of Ethyl, dihydroquinidine glutarate 3 as illustrated in Figure 2. 1,3-Dicyclohexylcarbodiimide (DCC, 0.153 g, 0.742 mmol) was added to a mixture of absolute ethanol (0.0113 g, 0.245 mmol), DMAP (0.0150 g, 0.123 mmol), and the dihydroquinidine glutarate (mono-ester) 6 (0.324 g, 0.736 mmol) in methylene chloride. The reaction mixture was stirred until the dihydroquinidine glutarate (mono-ester) 6 disappeared as determined by thin layer chromatography (TLC; the reaction typically took approximately 3 h). The reaction mixture was filtered through celite to allow removal of urea precipitate, and the product was isolated after evaporation of the solvent. The residue was purified by column chromatography (methylenechloride: methanol = 9: 1) to give 3 (0.109 g, 95.1 %): ^{1}H-NMR (300 MHz, CDCl$_3$) d 0.87 (t, J = 7 Hz, 3H), 1.35 (m, 1H), 1.16 (t, J = 7 Hz, 3 H), 1.3-1.6 (m, 7H), 1.75-2.00 (m, 3H), 2.43 (t, J = 7 Hz, 2H), 2.6-3.0 (m, 3H), 3.24 (q, J = 7 Hz, 1H), 3.92 (s, 3H), 4.05 (q, J = 7 Hz, 2H), 6.62 (d, J = 7 Hz, 1H), 7.26 (d, J = 3 Hz, 1H), 7.32 (dd, J = 9, 3 Hz, 1H), 7.42 (d, J = 4 Hz, 1H), 7.93 (d, J = 9 Hz, 1H), 8.69 (d, J = 4 Hz, 1H); ^{13}C-NMR (75 MHz, CDCl$_3$) d 11.7, 14.1, 19.9, 22.3, 25.2, 25.7, 26.3, 33.0, 33.2, 36.6, 49.6, 50.3, 55.9, 58.7, 60.3, 72.7, 101.1, 118.0, 122.1, 126.6, 131.6, 143.1, 144.5, 147.1, 158.1, 171.4, 172.7; HRMS (FAB) calcd. for [C$_{27}$H$_{36}$N$_2$O$_5$ + H$^+$] 469.2702, found 441.2718.

Synthesis of p lyethylene glycol, dihydroquinidine glutarate 2 as illustrated in Figure 2. DCC (0.153 g,

- 31 -

0.742 mmol) was added to a mixture of polyethylene
glycol (1.23 g, 0.246 mmol), DMAP (0.0150 g, 0.123
mmol), and dihydroquinidine glutarate (mono-ester) **6**
(0.324 g, 0.736 mmol) in methylene chloride. The
5   reaction mixture was stirred for 6 h and the urea
precipitate was removed by filtration through celite.
Diethyl ether was slowly added to the filtrate with a
vigorous stirring, and a precipitate formed from was
isolated as a white solid. This material was washed
10   with absolute ethanol and diethyl ether, then dried over
P_2O_5 *in vacuo* (1.29 g, 96.0 %). ^{1}H-NMR (300 MHz, $CDCl_3$) δ
0.98 (t, J = 7 Hz, 3H), 1.40 (m, 1H), 1.6-2.7 (m, 17H),
3.11 (q, J = 7 Hz, 1H), 3.2-3.9 (polyethylene glycol
peaks), 4.13 (s, 3H), 4.20 (t, J = 7 Hz, 2H), 7.23 (d, J
15   = 3 Hz, 1H), 7.39 (dd, J = 9, 3 Hz, 1H), 7.59 (s, 1H),
7.80 (s, 1H), 8.05 (d, J = 9 Hz, 1H), 8.65 (d, J = 4 Hz,
1H).
Procedure for asymmetric dihydroxylation wherein
representative substrates, product yields and ee's are
20   **tabulated in Figure 3.** A small aliquot (catalytic
amount) of OsO_4 in *t*-butanol (22 ml of OsO4 2.5 wt %
solution) was added to a mixture of the polymer catalyst
(0.300 g, 54.9 mmol), 4-methylmorpholine N-oxide (0.0386
g, 0.329 mmol), and tetraethylammonium acetate
25   tetrahydrate (0.0574 g, 0.220 mmol) in acetone-water
(10/1, v/v, 4 ml) at 4 °C. After stirring for 10 min,
the olefin (4 eq. relative to the polymer ligand) was
added either in one portion or by a slow addition. The
reaction mixture was stirred at 4 °C until the olefin
30   disappeared as judged by TLC. Next, solid sodium
metabisulfate (0.500 g) was added, and the mixture was
stirred for an additional 5 min, then diluted with
methylene chloride (10 ml) and dried over Na_2SO_4. All
solids were removed by filtration and washed three times
35   with methylene chloride (3 x 5 ml). The combined
filtrates were evaporated to half volume and diethyl
ether was slowly added to the mixture under vigorous

stirring conditions. The precipitate obtained was collected on a glass filter, washed with absolute ethanol/ethyl ether, and dried in vacuo (0.294 g, 98 % recovery of ligand resulted from this procedure).

5   Reduction in vacuo of the filtrate gave nearly pure dihydroxylated product. The enantiomeric excess of the diol was determined either by HPLC of the bis-acetate of hydrobenzoin on a Pirkle 1A ionic D-phenylglycine column or through NMR analysis of the derived bis-Mosher ester.

10

General Synthesis of Compounds 7 - 10 (as shown in Figure 4): *Trans*-cinnamic acid (1.1 equivalents; Aldrich) was coupled to each heterogeneous resin (1.0 equivalents) with the aide of EDC/DMAP coupling agents

15   (1.2 equivalents EDC / 0.10 equivalents DMAP) in 0.10 Molar methylene chloride. For the soluble polymer MeO-PEG, a DCC/DMAP (1.2 equivalents EDC / 0.10 equivalents DMAP) combination was used for the preparation of **10**. Upon reaction completion (approximately 12 hours at 25

20   °C), the urea formed was removed by filtration. To the filtrate was added diethyl ether and **10** was separated as a white solid from the mixture. The loading of *trans*-cinnamic acid onto each polymer was determined to be >98 % by measuring the release of cinnamic acid and its

25   methyl ester from the polymers with TFA/CH$_2$Cl (v/v, 95/5) and sodium methoxide in methanol respectively.

Procedure for asymmetric dihydroxylation for ol finic
substrates attached to polymeric supports (example using
polymer bound olefins) (Figures 5-6):

5   <u>Method A</u>:

A small aliquot of OsO_4 in *t*-butanol (OsO_4 2.5 wt %
solution, see Figure 6 for the amount used in each
reaction) was added to a mixture of the ligand (ligands
13 or 14 of Figure 5 or ligands 2 or 3 of Figure 2),

10   $K_3Fe(CN)_6$ (0.250 g, 6 eq. relative to the olefin), K_2CO_3
(0.052 g, 3 eq.), and methanesulfonamide (0.012 g, 1
eq.) in *t*-butanol-water (1/1, v/v, 4 ml) at room
temperature. Alternatively, the following ligands as
described in the following U.S. Patents can be used in

15   lieu of ligands 13, 14, 2, or 3:
1. from U.S. Patent No. 5,260,461, incorporated herein
by reference:
1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
1,4-bis-(9'-O-quinidyl)-phthalazine;

20   3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-
(9'-O-dihydroquinyl)-phthalazine;
1,4-bis-(9'-O-quinyl)-phthalazine;
3,6-bis-(9'-O-dihydroquinyl)-pyridazine;

25   3,6-bis-(9'-O-quinyl)-pyridazine;
2. from U.S. Patent No. 4,871,855, incorporated herein
by reference:
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinidine;

30   4-methoxybenzoyl dihydroquinidine;
4-chlorobenzoyl dihydroquinidine;
2-chlorobenzoyl dihydroquinidine;
4-nitrobenzoyl dihydroquinidine;
3-chlorobenzoyl dihydroquinidine;

35   2-methoxybenzoyl dihydroquinidine;
3-methoxybenzoyl dihydroquinidine;
2-naphthoyl-dihydroquinidine;

- 34 -

cyclohexanoyl dihydroquinidine;

p-phenylbenzoyl dihydroquinidine;

dimethylcarbamoyl dihydroquinidine;

benzoyl dihydroquinine;

4-methoxybenzoyl dihydroquinine;

4-chlorobenzoyl dihydroquinine;

2-chlorobenzoyl dihydroquinine;

4-nitrobenzoyl dihydroquinine;

3-chlorobenzoyl dihydroquinine;

2-methoxybenzoyl dihydroquinine;

3-methoxybenzoyl dihydroquinine;

2-naphthoyl dihydroquinine;

cyclohexanoyl dihydroquinine;

p-phenylbenzoyl dihydroiquinone;

3. From U.S. Patent No. 5,126,494, incorporated herein
by reference:

acrylonitrile co-polymer of 9-(4-
chlorobenoyloxy)-quinidine;

acrylonitrile co-polymer of 11-((2-
acryloyloxy)ethyl-sulfinyl)-9-(4-
chlorobenoyloxy)-10,11-dihydroquinidine;

acrylonitrile co-polymer of 11-[2-
acryloyloxy)ethylsulfonyl]-9-(N,N-
dimethylcarbamoyl)-10,11-dihydroquinidine;

acrylonitrile co-polymer of 9-(10-undecanoyl)-
10,11-dihydroquinidine.

After stirring for 10 min, the polymer bound olefin
(0.125 mmol, 1 eq.) was added in one portion. The
reaction mixture was stirred for 24 hrs. To the
reaction mixture was added solid sodium metabisulfate
(0.400 g), and the mixture was stirred for an additional
5 min. The reaction mixture was filtered, and
successively washed with acetone and methylene chloride.
The resin was dried over Na_2SO_4 under vacuo. i) The
resin was suspended in TFA/CH_2Cl_2 (v/v, 95/5) for 30 min.
After filtering off the resin, the filtrate was

evaporated to dryness. The % conversion of the olefin
to the dihydroxylated product was determined by NMR. A
comparision of 'H olefinic signals of the unreacted
cinnamic acid with aliphatic proton signals of the
5   product diol acid allowed assessment of the percent
conversion. ii) The resin was suspended in a methanol
solution of sodium methoxide. This mixture was stirred
for 2 h at room temperature and the solvent was removed
in vacuo. The mixture was separated by silica gel
10   column chromatography (ethyl acetate/hexane, 1/1). The
enantiomeric excess of the product diol was determined
through NMR analysis of the derived bis-Mosher ester of
this methyl ester.

15   Method B:

        A similar procedure to Method A was followed except
acetone/water solvent and methylmorpholine *N*-oxide (NMO)
were used. The reaction mixture contained a small
aliquot of OsO$_4$ in *t*-butanol (OsO$_4$ 2.5 wt % solution, 13
20   μl, 0.01 eq. relative to the olefin), the ligand (0.0025
g, 0.025 eq.), 4-methylmorpholine *N*-oxide (0.022 g, 1.5
eq.), and tetraethylammonium acetate tetrahydrate (0.033
g, 1.0 eq.) in acetone-water (10/1, v/v, 4 ml) at 4 °C.

25   **Synthesis of compound 18 as illustrated in Figure 7.** A
mixture of dihydroquinidine **15** (5.00 g, 15.32 mmol, 1
eq; Aldrich), 1,4-dichlorophthalazine **16** (3.66 g, 18.38
mol, 1.2 eq; Aldrich), and K$_2$CO$_3$ (6.35 g, 45.95 mmol, 3
eq) in dry toluene are refluxed with a concurrent
30   azeotropic removal of water for 2 hr. Then, 85 % KOH
pellets (3.02 g, 45.95 mmol, 3 eq) was added at once and
the reaction mixture was refluxed until dihydroquinidine
disappeared on t.l.c. The light orange solution was
cooled to room temeperature, mixed with water, and then
35   extracted with ethyl acetate. The organic layer was
dried over sodium sulfate. The removal of solvent and
then column chromatogarphy of residue gave the mono-

substituted chlorophthalazine **17** (6.05 g, 81 %), which upon similar transformation with quinidine provided the di-substituted phthalazine **18** (6.76 g, 85 % starting from 5.00 g of **17**).   **17**: ^{1}NMR (300 MHz, CDCl$_3$) δ 0.91 (t, J = 6.7 Hz, 3H), 1.40-1.70 (m, 6H), 1.77 (m, 1H), 2.12 (m, 1H), 2.65-3.00 (m, 4H), 3.43-3.58 (m, 1H), 3.99 (s, 3H), 7.27 (d, J = 7.0 Hz, 1H), 7.34 (dd, J = 9.3 & 2.8 Hz, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.62 (d, J = 2.7 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 8.00 (m, 2H), 8.13-8.20 (m, 1H), 8.33-8.42 (m, 1H), 8.64 (d, J =4.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 11.9, 23.5, 25.4, 26.1, 27.1, 37.3, 49.9, 50.9, 55.5, 59.9, 101.7, 118.5, 121.4, 121.8, 122.8, 122.9, 125.3, 127.7, 128.2, 131.6, 133.0, 133.3, 144.0, 144.7, 147.0, 147.2, 150.5, 157.7; HRMS (FAB$^+$) calcd for [C$_{28}$H$_{29}$ClN$_4$O$_2$ + H$^+$] = 489.2057, found = 489.2051.   **18**: ^{1}NMR (300 MHz, CDCl$_3$) δ 0.78 (t, J = 6.7 Hz, 3H), 1.20-1.65 (m, 10H), 1.68 (m, 1H), 1.85-2.30 (m, 3H), 2.55-3.00 (m, 8H), 3.39 (m, 2H), 3.88 (s, 6H), 4.97 (m, 2H), 5.90 (m, 1H), 6.95 (d, J = 6.5 Hz, 1H), 7.01 (d, J = 5.9 Hz, 1H), 7.34 (m, 2H), 7.40 (d, J = 4.6 Hz, 1H), 7.42 (d, J = 4.6 Hz, 1H), 7.52 (d, J = 2.7 Hz, 1H), 7.54 (d, J = 2.6 Hz, 1H), 7.91 (m, 2H), 7.96 (d, J = 9.2 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 8.31 (m, 2H), 8.61 (d, J = 4.5 Hz, 1H), 8.62 (d, J = 4.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 11.8, 23.2, 23.4, 25.2, 26.0, 26.2, 26.4, 27.2, 27.7, 37.3, 39.6, 49.4, 49.8, 49.9, 50.8, 55.5, 60.0, 60.2, 76.0, 77.2, 101.9, 102.0, 114.6, 118.2, 118.4, 121.7, 121.8, 122.3, 122.7, 123.0, 127.3, 128.1, 129.0, 131.4, 131.5, 132.0, 132.1, 140.3, 144.6, 144.8, 144.9, 147.3, 156.3, 156.4, 157.5, 157.6; HRMS (FAB$^+$) calcd for [C$_{48}$H$_{52}$N$_6$O$_4$ + H$^+$] = 777.4128, found 777.4104.

Synthesis of Compound 19 as illustrated in Figure 7.
The heating of **18** (6.00 g, 7.73 mmol, 1 eq) and 3-mercaptopropionic acid (3-MPA, 0.821 g, 7.74 mmol, 1 eq) in the presence of 2,2'-azobisisobutyronitrile (AIBN,

— 37 —

0.0635 g, 0.3867 mmol, 0.05 eq) in benzene (70 °C)
allowed the isolation of **19** as a tan precipitate (4.43
g, 64 %). This precipitate was already such pure that
it was used for the next step without further
5   purification. **19**: ^{1}NMR (300 MHz, CDCl$_3$) δ 0.86 (t, J =
6.7 Hz, 3H), 1.25-3.25 (m, 30H), 3.50 (m, 2H), 3.89 (s,
3H), 3.97 (s, 3H), 6.60 (broad s, 1H), 7.30 (m, 3H),
7.44 (t, J = 4.4 Hz, 2H), 7.49 (broad s, 1H), 7.53 (d, J
= 2.3, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.88 (m, 2H), 7.95
10   (d, J = 9.2 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 8.19 (d,
J = 8.1 Hz, 1H), 8.27 (d, J = 7.7 Hz, 1H), 8.59 (d, J =
4.6 Hz, 1H), 8.64 (d, J = 4.5 Hz, 1H); HRMS (FAB$^+$) calcd
for [C$_{51}$H$_{58}$N$_6$O$_6$S + H$^+$] = 883.4216, found 883.4242.

15   **Synthesis of Compound 20 as illustrated in Figure 7.** A
mixture of acid **19** (1.00 g, 1.13 mmol, 1.5 eq), MeO-PEG-
NH$_2$ (3.78 g, 0.756 mmol, 1 eq), N,N-
dimethylaminopyridine (DMAP, 0.0231 g, 0.189 mmol, 0.25
eq) and 1,3-dicyclohexylcarbodiimide (DCC, 0.233 g, 1.13
20   mmol, 1.5 eq) in methylene chloride (DCM) was stirred
overnight at room temperature. After the reaction was
complete, the insoluble urea side-product was removed by
filtration and the pegylated ligand **20** (4.34 g, 98 %)
was isolated from the reaction mixture by precipitation
25   following a slow addition of diethyl ether. **20**: ^{1}NMR
(300 MHz, CDCl$_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.25-2.85
(m, 30H), 3.20-3.75 (PEG peaks), 3.84 (t, J = 6.5 Hz,
2H), 3.88 (s, 6H), 6.59 (broad t, 1H), 6.90 (d, J = 6.6
Hz, 1H), 6.97 (d, J = 5.7Hz, 1H), 7.30 (dd, J = 9.2 &
30   2.4 Hz, 1H), 7.32 (dd, J = 9.0 & 2.4 Hz, 1H), 7.39 (t, J
= 4.6 Hz, 2H), 7.47 (d, J = 2.5 Hz, 1H), 7.51 (d, J =
2.5 Hz, 1H), 7.90 (m, 2H), 7.93 (d, J = 9.0 Hz, 1H),
7.94 (d, J = 9.2 Hz, 1H), 8.28 (m, 2H), 8.59 (d, J = 4.5
Hz, 2H).

35

Synthesis f Compound 14 as illustrated in Figure 7. To
the mixture of the sulfide **20** (4.00 g, 0.682 mmol, 1eq),

and *N*-methylmorpholine-*N*-oxide (NMO, 0.24 g, 2.046 mmol,
3 eq) in acetone/water (v/v, 2/1) was added OsO₄ (1 mol
%, 0.01 eq). The resulting reaction mixture was stirred
overnight at room temperature, and then quenched with
sodium bisulfide (100 mg). The reaction mixture was
dried over sodium sulfate, and solid was filtered off.
Slow addition of ether to the filtrate separated **14** as a
white precipitate (3.90 g, 97 %). **14:** ¹NMR (300 MHz,
CDCl₃) δ 0.79 (3H), 1.10-3.00 (30H), 3.10-3.80 (PEG
peaks), 3.80-4.00 (8H), 6.70 (1H), 6.95 (1H), 7.05 (1H),
7.20-7.45 (7H), 7.50 (1H), 7.80-8.10 (4H), 8.28 (1H),
8.37 (1H), 8.55 (2H). Peak mutiplicity was not further
characterized due to line-broadening.

**General procedure for the attachment of PEG soluble
support to the ligand:**

A mixture of ligand acid (1.00 g, 1.13 mmol, 1.5
eq., MeO-PEG-NH₂ (3.78 g, 0.756 mmol, 1 eq; Aldrich/
Sigma/ Fluka, etc.), N,N- dimethylaminopyridine (DMAP,
0.0231 g, 0.189 mmol, 0.25 eq) and 1,3-
dicyclohexylcarbodiimide (DCC, 0.233 g, 1.13 mmol, 1.5
eq) in methylene chloride (DCM) was stirred overnight at
room temperature. After the reaction was complete, the
insoluble urea side-product was removed by filtration
and the pegylated ligand (4.34 g, 98 %) was isolated
from the reaction mixture by precipitation following a
slow addition of diethyl ether. Ligand acid can be
obtained as described in the following U.S. Patents:
1. from U.S. Patent No. 5,260,461, incorporated herein
   by reference, ligand acids may be obtained for the
   following alkaloids:
   1,4-bis-(9'-O-dihydroquinidyl)-phthalazine;
   1,4-bis-(9'-O-quinidyl)-phthalazine;
   3,6-bis-(9'-O-dihydroquinidyl)-pyridazine;
   3,6-bis-(9'-O-quinidyl)-pyridazine; 1,4-bis-
   (9'-O-dihydroquinyl)-phthalazine;
   1,4-bis-(9'-O-quinyl)-phthalazine;

- 39 -

3,6-bis-(9'-O-dihydroquinyl)-pyridazine; and
3,6-bis-(9'-O-quinyl)-pyridazine;

2. from U.S. Patent No. 4,871,855, incorporated herein
by reference, ligand acids may be obtained for the
following alkaloids:

dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinidine;
4-methoxybenzoyl dihydroquinidine;
4-chlorobenzoyl dihydroquinidine;
2-chlorobenzoyl dihydroquinidine;
4-nitrobenzoyl dihydroquinidine;
3-chlorobenzoyl dihydroquinidine;
2-methoxybenzoyl dihydroquinidine;
3-methoxybenzoyl dihydroquinidine;
2-naphthoyl-dihydroquinidine;
cyclohexanoyl dihydroquinidine;
p-phenylbenzoyl dihydroquinidine;
dimethylcarbamoyl dihydroquinidine;
benzoyl dihydroquinine;
4-methoxybenzoyl dihydroquinine;
4-chlorobenzoyl dihydroquinine;
2-chlorobenzoyl dihydroquinine;
4-nitrobenzoyl dihydroquinine;
3-chlorobenzoyl dihydroquinine;
2-methoxybenzoyl dihydroquinine;
3-methoxybenzoyl dihydroquinine;
2-naphthoyl dihydroquinine;
cyclohexanoyl dihydroquinine; and
p-phenylbenzoyl dihydroiquinone;

3. From U.S. Patent No. 5,126,494, incorporated herein
by reference, ligand acids may be obtained for the
following alkaloids:

acrylonitrile co-polymer of 9-(4-
chlorobenoyloxy)-quinidine;
acrylonitrile co-polymer of 11-((2-
acryloyloxy)ethyl-sulfinyl)-9-(4-
chlorobenoyloxy)-10,11-dihydroquinidine;

SUBSTITUTE SHEET (RULE 26)

- 40 -

acrylonitrile co-polymer of 11-[2-
acryloyloxy)ethylsulfonyl]-9-(N,N-
dimethylcarbamoyl)-10,11-dihydroquinidine; and
acrylonitrile co-polymer of 9-(10-undecanoyl)-
10,11-dihydroquinidine.

5

- 41 -

General procedure for asymmetric dihydroxylation using ligands attached to PEG support:

<u>Method A</u>:

A small aliquot of OsO$_4$ in t-butanol (OsO$_4$ 2.5 wt %
5   solution, 0.01-0.1 eq) was added to a mixture of
K$_3$Fe(CN)$_6$ (0.250 g, 6 eq. relative to the olefin), K$_2$CO$_3$
(0.052 g, 3 eq.), methanesulfonamide (0.012 g, 1 eq.),
and the PEG-bound alkaloid ligand **14** (0.025-0.25 eq.) or
any of the PEG-bound alkaloid ligands described above,
10   in t-butanol-water (1/1, v/v, 4 ml) at room temperature.
After stirring for 10 min, the olefin substrate (0.125
mmol, 1 eq.was added in one portion. Permissible
substrates include all classes of primary, secondary,
tertiary and quaternary substituted olefins described
15   in the prior art for the AD reaction. The reaction
mixture was stirred for 24 hours. The reaction mixture
was stirred at 4°C or room temperature until the olefin
disappeared as judged by TLC. Next, solid sodium
metabisulfate (0.500 g) was added, and the mixture was
20   stirred for an additional 5 min, then diluted with
methylene chloride (10 ml) and dried over Na$_2$SO$_4$. All
solids were removed by filtration and washed three times
with methylene chloride (3 x 5 ml). The combined
filtrates were evaporated to half volume and diethyl
25   ether was slowly added to the mixture under vigorous
stirring conditions. The precipitate obtained was
collected on a glass filter, washed with absolute
ethanol/ethyl ether, and dried *in vacuo* (0.294 g, 98 %
recovery of ligand resulted from this procedure).
30   Reduction *in vacuo* of the filtrate gave nearly pure
dihydroxylated product. The enantiomeric excess of the
diol was determined either by HPLC of the *bis*-acetate of
hydrobenzoin on a Pirkle 1A ionic *D*-phenylglycine column
or through NMR analysis of the derived bis-Mosher ester.

35

<u>Method B</u>:

A small aliquot (catalytic amount) of OsO$_4$ in t-

butanol (0.01-0.1 eq) was added to a mixture of the
polymer catalyst (PEG-ligand; see Method A for examples
of compounds used) (0.025-0.25 eq), 4-methylmorpholine
N-oxide (1.5 eq), and tetraethylammonium acetate
tetrahydrate (1 eq) in acetone-water (10/1, v/v, 4 ml)
at 4 °C. After stirring for 10 min, the olefin (1 eq)
was added either in one portion or by a slow addition.
The reaction mixture was stirred at 4 °C until the
olefin disappeared as judged by TLC. Next, solid sodium
metabisulfate (0.500 g) was added, and the mixture was
stirred for an additional 5 min, then diluted with
methylene chloride (10 ml) and dried over Na_2SO_4. All
solids were removed by filtration and washed three times
with methylene chloride (3 x 5 ml). The combined
filtrates were evaporated to half volume and diethyl
ether was slowly added to the mixture under vigorous
stirring conditions. The precipitate obtained was
collected on a glass filter, washed with absolute
ethanol/ethyl ether, and dried in vacuo (0.294 g, 98 %
recovery of ligand resulted from this procedure).
Reduction in vacuo of the filtrate gave nearly pure
dihydroxylated product. The enantiomeric excess of the
diol was determined either by HPLC of the bis-acetate of
hydrobenzoin on a Pirkle 1A ionic D-phenylglycine column
or through NMR analysis of the derived bis-Mosher ester.

- 43 -

What is claimed is:

1. An improved process for catalyzing a hydroxylation
reaction, the process being of a type which includes a
step for admixing, within a reaction medium, an olefin,
an agent, a catalyst for catalyzing the hydroxylation
reaction, and an alkaloid ligand for accelerating the
catalysis of the hydroxylation reaction, wherein the
improvement comprises:
      in said admixing step, the ligand is a PEG bound
          alkaloid ligand, the PEG bound alkaloid ligand
          being soluble in the reaction medium and
          precipitable in a precipitation medium.

2. An improved process for catalyzing a hydroxylation
reaction as described in claim 1 wherein the
hydroxylation reaction is an asymmetric dihydroxylation
reaction and the PEG bound alkaloid ligand is chiral.

3. In a process for catalyzing an hydroxylation
reaction,
      Step A: admixing an olefin, an agent, a catalyst
          for catalyzing the hydroxylation reaction, and
          an alkaloid ligand for accelerating the
          catalysis of the hydroxylation reaction, said
          admixing occurring in a reaction medium under
          reaction conditions for producing an
          hydroxylation product; then
      Step B: admixing a precipitation medium with the
          reaction medium of said Step A for
          precipitating the PEG bound alkaloid ligand;
          and then
      Step C: separating the precipitated PEG bound
          alkaloid ligand of said Step B from the
          hydroxylation product for recovering the PEG
          bound alkaloid ligand.

- 44 -

4. In a process for catalyzing an hydroxylation reaction
as described in claim 3,
in said step A, the hydroxylation reaction is an
asymmetric dihydroxylation reaction and
5   in said steps A, B, and C, the PEG bound alkaloid
ligand is chiral.

5. In a process for catalyzing an hydroxylation
reaction,
10   Step A: admixing one or more reactants with a
catalyst for catalyzing the hydroxylation
reaction and with a PEG bound alkaloid ligand
for accelerating the catalysis of the
hydroxylation reaction, said admixing
15   occurring in a reaction medium under reaction
conditions for producing an hydroxylation
product; then
Step B: admixing a precipitation medium with the
reaction medium of said Step A for
20   precipitating the PEG bound alkaloid ligand;
and then
Step C: separating the hydroxylation product of
said Step B from the precipitated PEG bound
alkaloid ligand for obtaing purified product.
25

6. In a process for catalyzing an hydroxylation reaction
as described in claim 5,
in said step A, the hydroxylation reaction is an
asymmetric dihydroxylation reaction and
30   in said steps A, B, and C, the PEG bound alkaloid
ligand is chiral.

7.   A PEG bound alkaloid ligand comprising:
a polyethylene glycol which is soluble in aqueous
35   medium and precipitable in aqueous/ether
medium, and
an alkaloid ligand coupled to said polyethylene

SUBSTITUTE SHEET (RULE 26)

- 45 -

glycol, said alkaloid ligand selected from a
group consisting of 1,4-bis-(9'-O-
dihydroquinidyl)-phthalazine; 1,4-bis-(9'-O-
quinidyl)-phthalazine; 3,6-bis-(9'-O-
dihydroquinidyl)-pyridazine; 3,6-bis-(9'-O-
quinidyl)-pyridazine; 1,4-bis-(9'-O-
dihydroquinyl)-phthalazine; 1,4-bis-(9'-O-
quinyl)-phthalazine; 3,6-bis-(9'-O-
dihydroquinyl)-pyridazine; 3,6-bis-(9'-O-
quinyl)-pyridazine; dimethylcarbamoyl
dihydroquinidine; benzoyl dihydroquinidine; 4-
methoxybenzoyl dihydroquinidine; 4-
chlorobenzoyl dihydroquinidine; 2-
chlorobenzoyl dihydroquinidine; 4-nitrobenzoyl
dihydroquinidine; 3-chlorobenzoyl
dihydroquinidine; 2-methoxybenzoyl
dihydroquinidine; 3-methoxybenzoyl
dihydroquinidine; 2-naphthoyl -
dihydroquinidine; cyclohexanoyl
dihydroquinidine; p-phenylbenzoyl
dihydroquinidine; dimethylcarbamoyl
dihydroquinidine; benzoyl dihydroquinine; 4-
methoxybenzoyl dihydroquinine; 4-chlorobenzoyl
dihydroquinine; 2-chlorobenzoyl
dihydroquinine; 4-nitrobenzoyl dihydroquinine;
3-chlorobenzoyl dihydroquinine; 2-
methoxybenzoyl dihydroquinine; 3-
methoxybenzoyl dihydroquinine; 2-naphthoyl
dihydroquinine; cyclohexanoyl dihydroquinine;
p-phenylbenzoyl dihydroiquinone; acrylonitrile
co-polymer of 9-(4-chlorobenoyloxy)-quinidine;
acrylonitrile co-polymer of 11-((2-
acryloyloxy)ethyl-sulfinyl)-9-(4-
chlorobenoyloxy)-10,11-dihydroquinidine;
acrylonitrile co-polymer of 11-[2-
acryloyloxy)ethylsulfonyl]-9-(N,N-
dimethylcarbamoyl)-10,11-dihydroquinidine;

SUBSTITUTE SHEET (RULE 26)

acrylonitrile co-polymer of 9-(10-undecanoyl)-
10,11-dihydroquinidine; and alkaloid ligand
represented by the following structures:
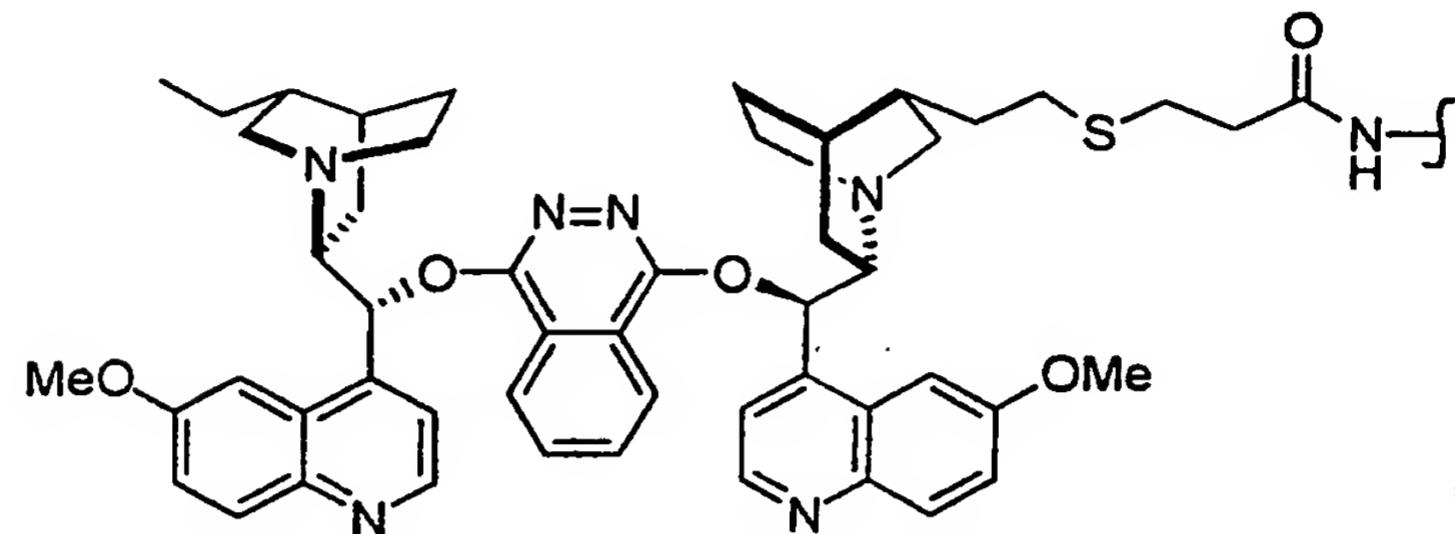
5
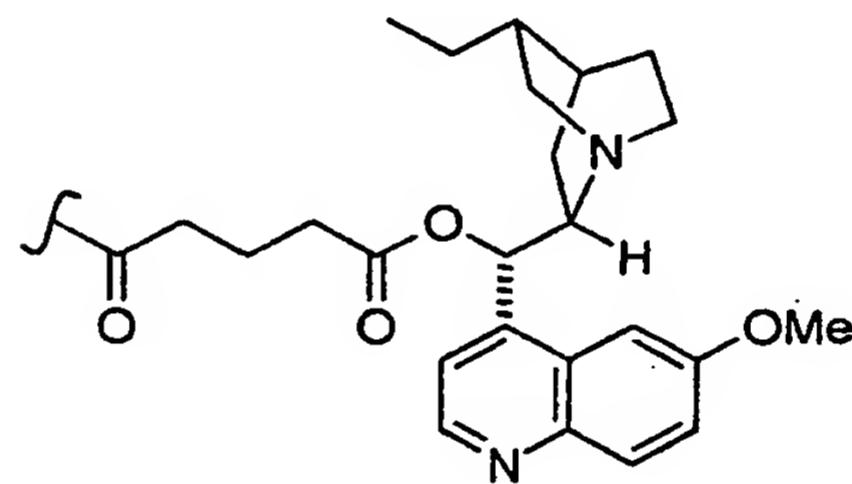
and
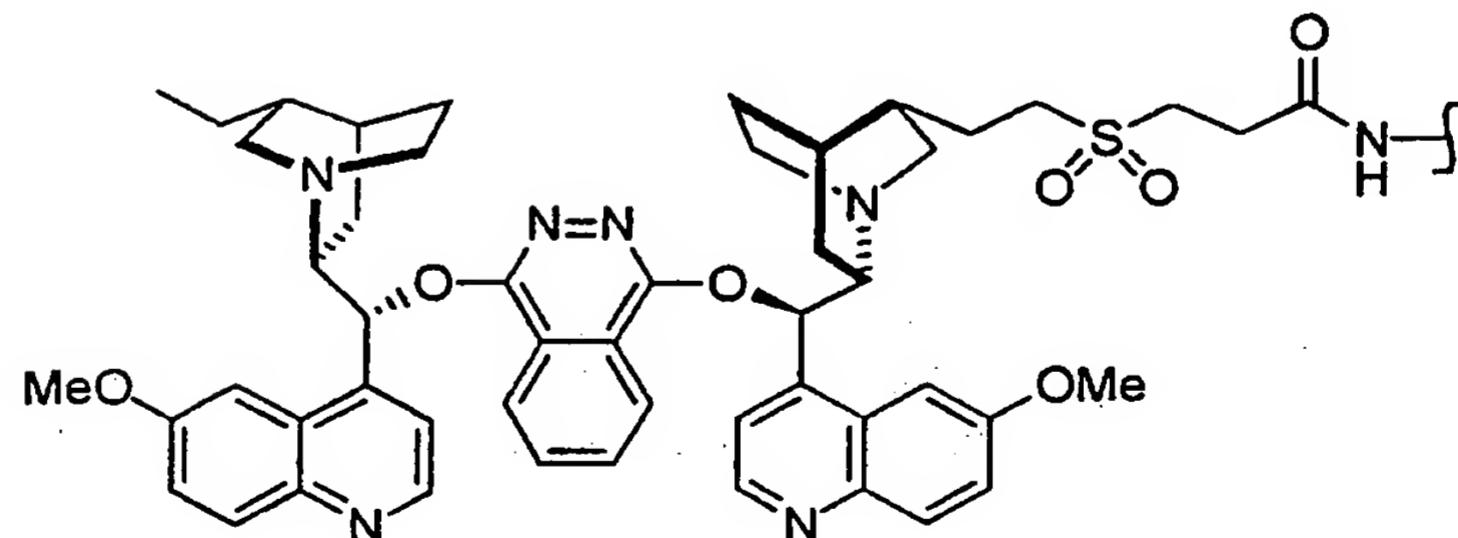
- 47 -

8.   A PEG bound alkaloid ligand as described in claim 7
wherein said alkaloid ligand is coupled to said
polyethylene glycol by a linkage selected from the group
consisting of ester linkage, amide linkage, thoester
linkage, ester linkage, thiether linkage, and sulphone
linkage.

9. A PEG bound alkaloid ligand as described in claim 7
represented by the following structure:

10. A PEG bound alkaloid ligand as described in claim 7
represented by the following structure:
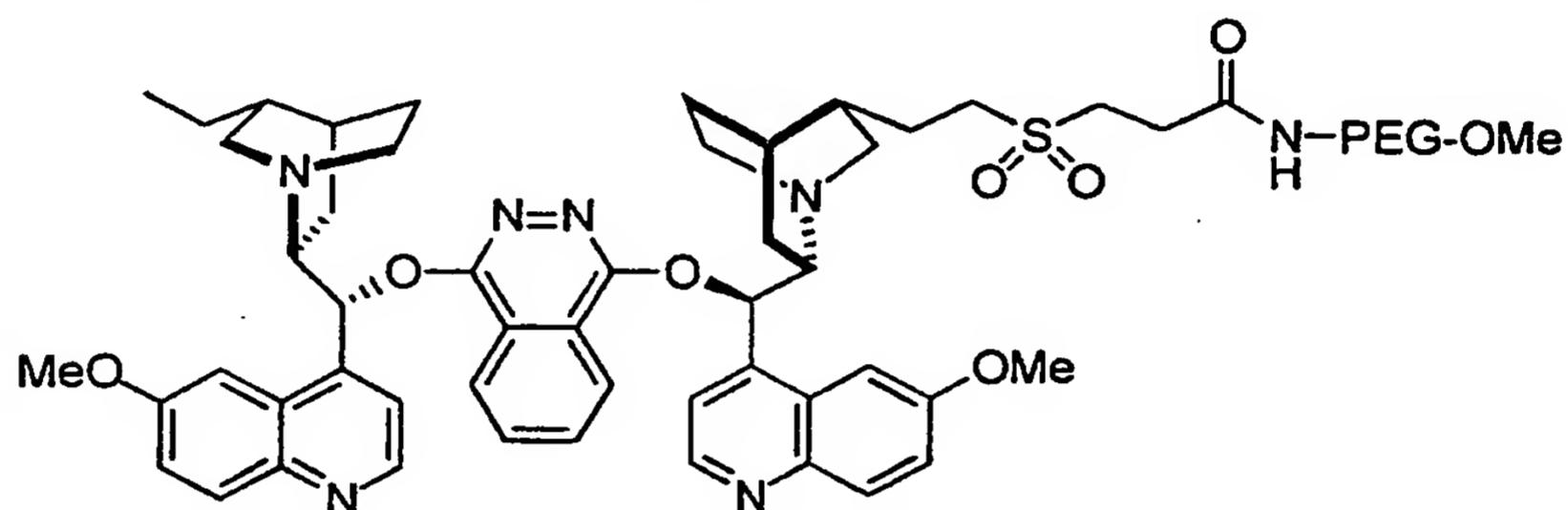
SUBSTITUTE SHEET (RULE 26)
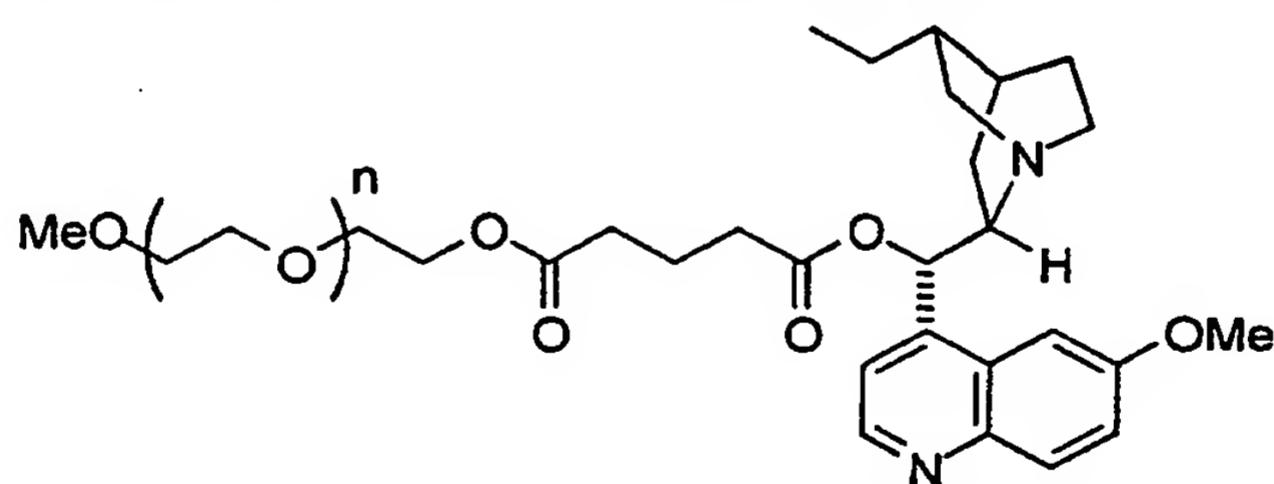
- 48 -

11. A PEG bound alkaloid ligand as described in claim 7 represented by the following structure:
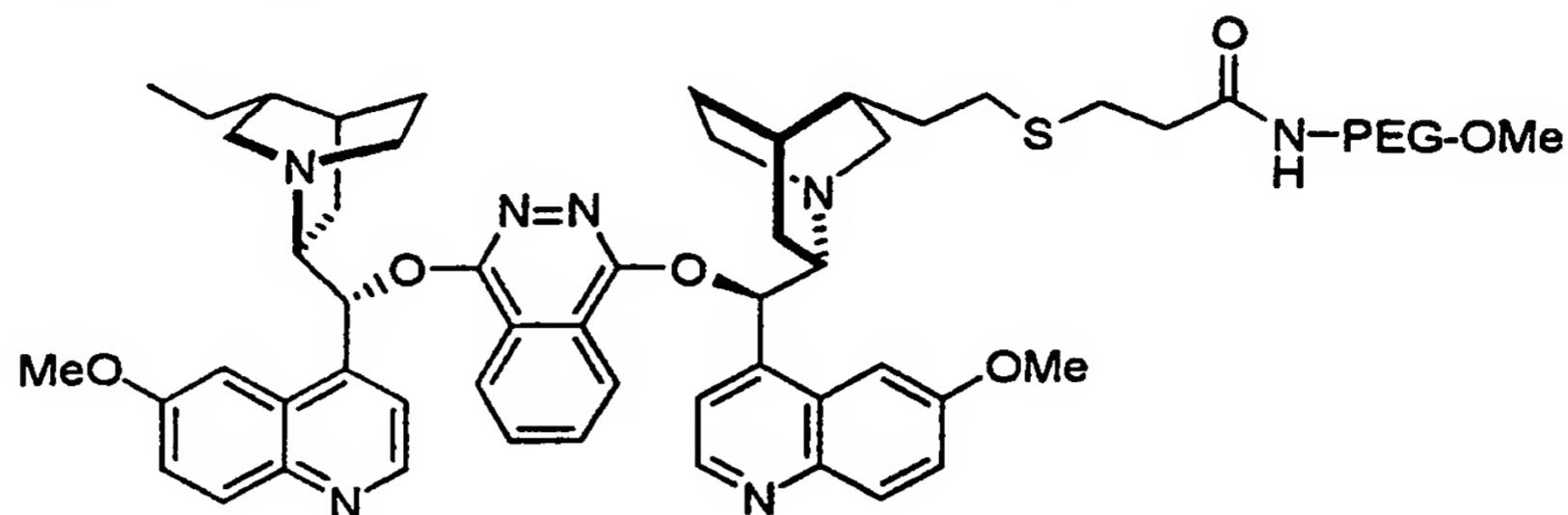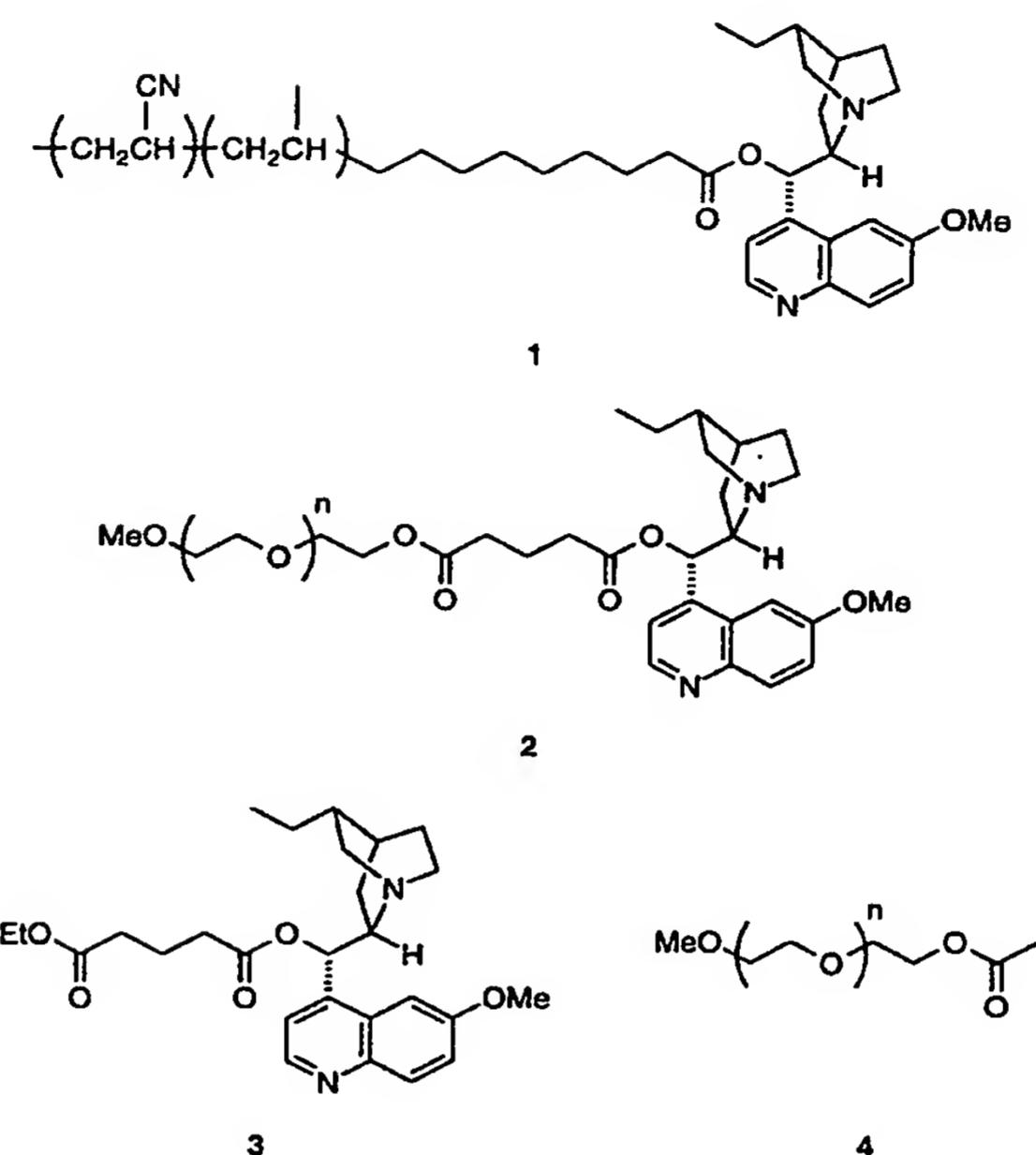
FIGURE 1
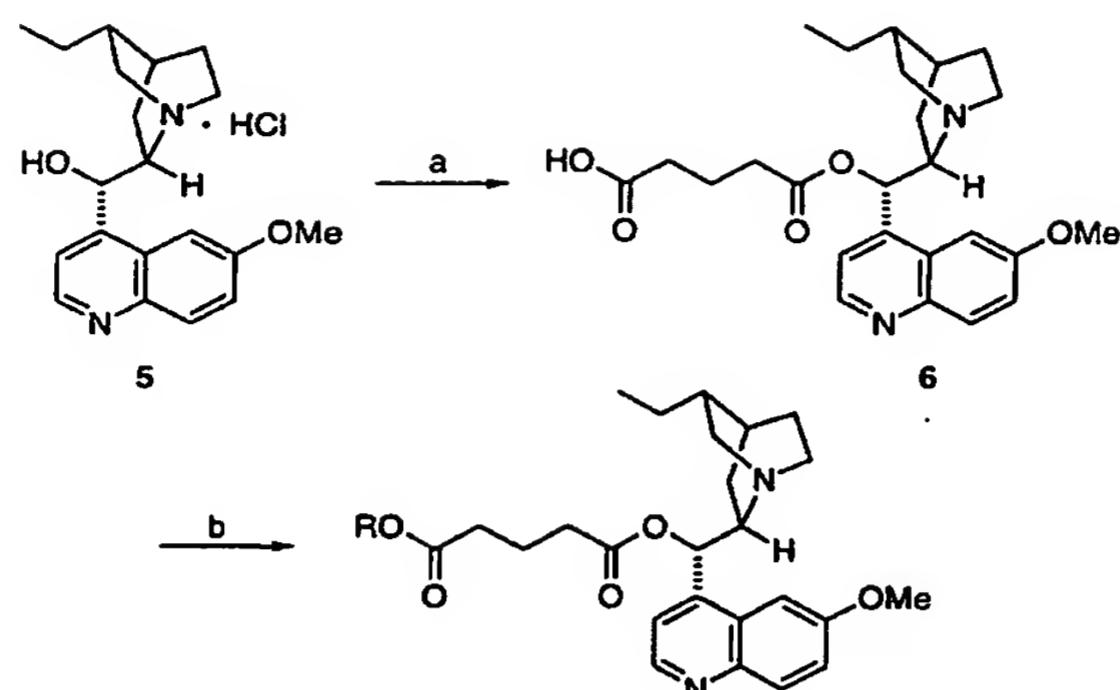
2; R = Polyethylene glycol
3; R = Ethyl

FIGURE 2

Entry	Catalyst	Olefin	Reaction Time	Yield (%)	ee (%)
1	1		48 h	87	82[b]
2	2.		4 h	89	88
3	2[c]		4 h	89	87
4	2[c]		4 h	89	88
5	2[c]		4 h	89	88
6	2[c]		4 h	89	87
7	2[c]		4 h	89	87
8	3		4 h	89	88
9	4		4 h[d]	5	0
10	2		5 h[e]	80	60
11	3		5 h[e]	80	60
12	2		5 h[e]	80	84
13	3		5 h[e]	80	85
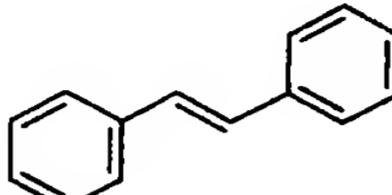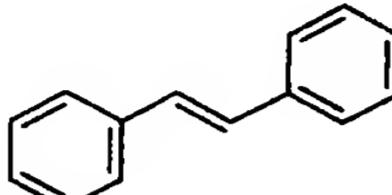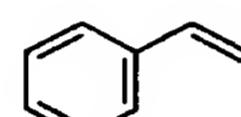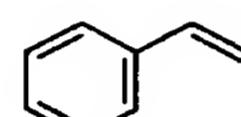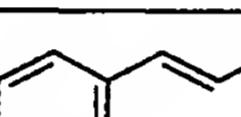
FIGURE 3

Merrifield Resin:

7

Wang Resin:

8

Tentagel Resin:

9

PEG:

10

11

FIGURE 4

7, 8, 9,
10 or 11 $\xrightarrow{\text{1. 13 or 14, OsO}_4,\ \text{K}_3\text{FeCN}_6\text{ or NMO}}{\text{2. Cleavage (H}^+\text{ or MeONa)}}$

(1)

12a: R = H
12b: R = Me

13: R = —H

14: R =
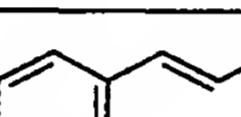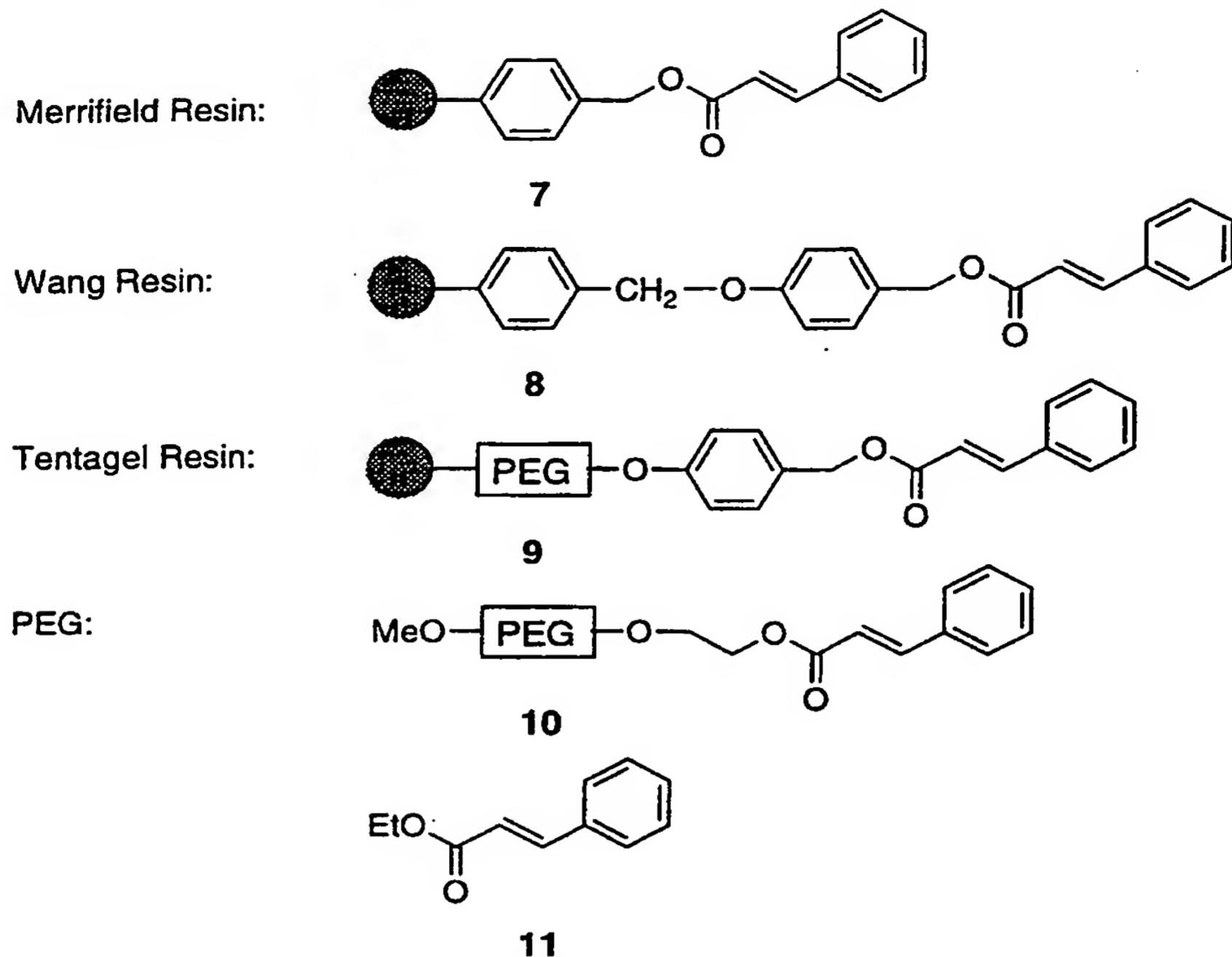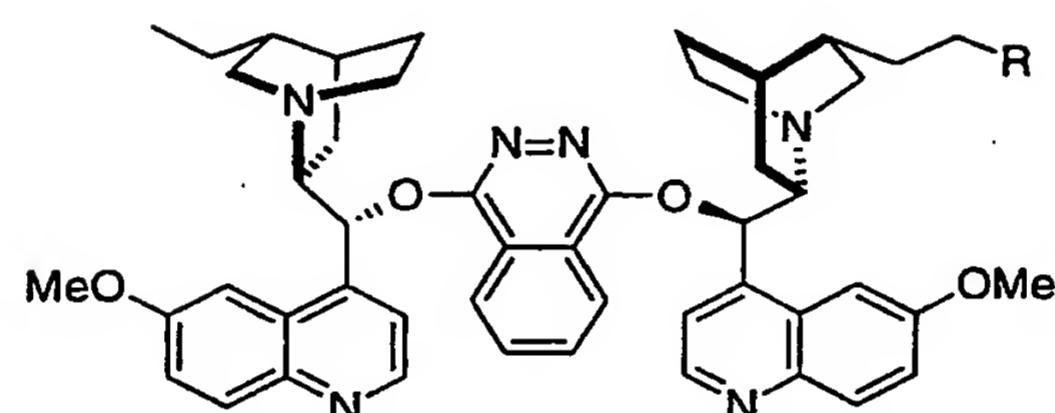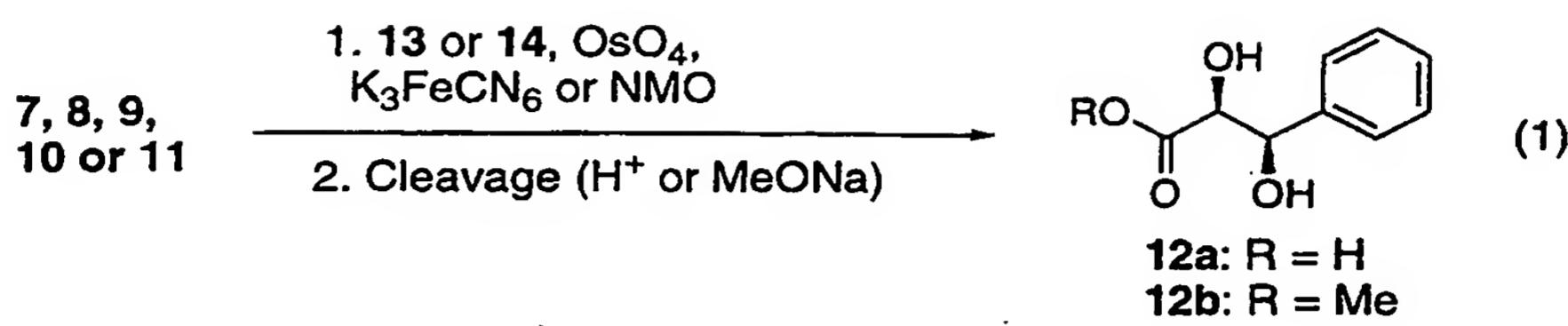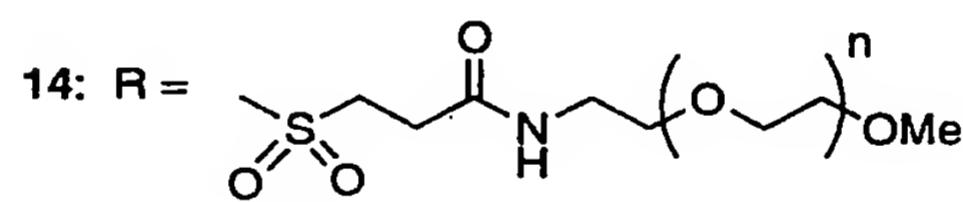
FIGURE 5

Entry	Polymer-olefin	Reaction time (hr)	OsO$_4$ [a]	Method [b]	% conversion [c]	ee [d]
1	7	72	0.01	A	–	–
2	8	72	0.01	A	–	–
3	9	24	0.01	A	3	99
4	9	24	0.02	A	63	98
5	9	24	0.10	A	96	99
6	10	0.5	0.10	A	100	99
7	7	24	0.01	B	100	88
8	8	24	0.01	B	100	90
9	9	24	0.01	B	100	87
10	10	24	0.008	A	80	97
11	11	24	0.008	A	100	97
12	9	24	0.02	A	60	98

FIGURE 6
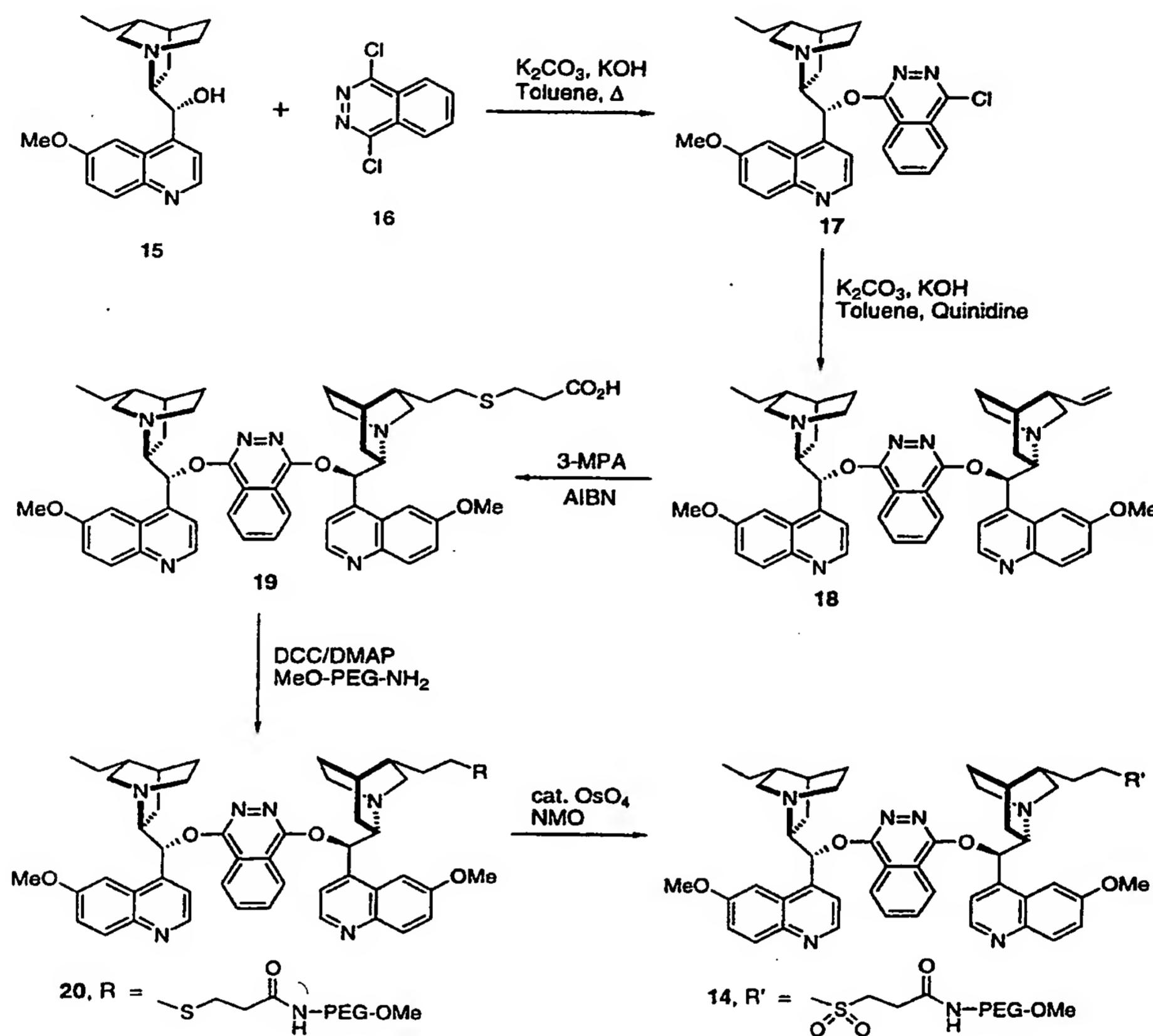
FIGURE 7

Entry	Olefin	Oxidant	Yield (%)	*ee (%)*
1	Ph⟍⟍	NMO	87	72
2		K_3FeCN_6	88	98 (97)[b]
3	Ph⟍⟍Me	NMO	87	91
4		K_3FeCN_6	83	99 (99)[b]
5	Ph⟍⟍Ph	NMO	98	94
6		K_3FeCN_6	95	99 (>99)[b]
7	n-Bu⟍⟍n-Bu	NMO	84	80
8		K_3FeCN_6	80	97 (97)[b]
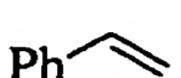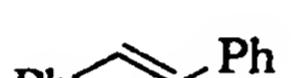
FIGURE 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/02442

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6)   :C07C 29/03 ; C07D 401/14 ; C07D 453/04

US CL   :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :   568/896 ; 544/233, 238, 240 ; 546/134

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 92/20677 A1 (MASSACHUSETTS INSTITUTE OF TECHNOLOGY) 26 November 1992, entire document.	1-11
A	COREY et al. ' Kinetic Investigations Provide Additional Evidence That an Enzyme-like Binding Pocket Is Crucial for High Enantioselectivity in the Bis-Cinchona Alkoid Catalyzed Assymetric Dihydroxylation of Olefins'. J. Am. Chem. Soc. January 1996, Vol 118, No. 2, pages 319-329, entire document.	1-11

☒ Further documents are listed in the continuation of Box C.   ☐   See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 APRIL 1997	23 APR 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer JEAN F. VOLLANO
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ZHANG et al. 'Nonlinear effects involving two competing psuedo-enantiomeric catalysts: example in asymmetric dihydroxylation of olefins'. Tetrahedron: Asymmetry. November 1995, Vol. 6, No. 11, pages 2637-2640, entire document.	7-11
A	SONG et al. 'Polymeric cinchona alkaloids for the heterogeneous catalytic asymmetric dihydroxylation of olefins: the influence of the polymer backbone polarity on the compatibility between polymer support and reaction medium' November 1995, Vol. 6, No.11, pages 2687-2694, entire document.	1-11

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

568/896 ; 544/233 ; 546/134

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, CAS ONLINE
search terms: hydroxylation reaction, alkaloid ligand, chiral, asymmetric, olefins, alkenes, peg, carbowax, ligand, cinchona, dihydroquinidine